

SCIENTIFIC ARTICLE

Influence of methylprednisolone on the reversal time of sugammadex: a randomized clinical trial



Merve Hayriye Kocaoğlu ^{a,*}, Başak Ceyda Meço ^b, Menekşe Özçelik ^b, Yeşim Batıslam ^b

^a Turkish Ministry of Health Ankara, 29 Mayıs State Hospital, Department of Anesthesiology and Intensive Care, Ankara, Turkey

^b Ankara University Faculty of Medicine, Department of Anesthesiology and Intensive Care, Ankara, Turkey

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Abstract

Background and objectives: Sugammadex is a modified gamma-cyclodextrin that reverses the effects of aminosteroidal neuromuscular blocking agents. Likewise, some steroid molecules, such as toremifene, fusidic acid, and flucloxacillin, can also be encapsulated by sugammadex. Methylprednisolone, which is a synthetic steroid used commonly for airway edema prophylaxis, can also be encapsulated by sugammadex. The objective of this study was to compare the recovery times of sugammadex for reversing rocuronium-induced moderate neuromuscular blockade in those who received intraoperative 1 mg kg⁻¹ methylprednisolone or saline.

Method: This single-centered, randomized, controlled, prospective study included 162 adult patients undergoing elective ear-nose-throat procedures (aged from 18 to 65, an ASA physical status I-II, a BMI less than 30 kg m⁻², and not taking steroid drug medication) with propofol, remifentanyl, rocuronium and sevoflurane. Neuromuscular monitoring was performed using calibrated acceleromyography. The Control Group (Group C) received 5 mL of saline, while the Methylprednisolone Group (Group M) received 1 mg kg⁻¹ of methylprednisolone in 5 mL of saline just after induction. After the completion of surgery, regarding the TOF count, two reappeared spontaneously and 2 mg kg⁻¹ sugammadex was administered to all patients. Recovery of the TOF ratio to 0.9 was recorded for both groups, and the estimated recovery time to reach a TOF ratio (TOFr) of 0.9 was the primary outcome of the study.

Results: Median time to TOFr = 0.9 was for 130.00 s (range of 29–330) for Group C and 181.00 s (100–420) for Group M ($p < 0.001$). The differences between the two groups were statistically significant.

Conclusion: When using 2 mg kg⁻¹ of sugammadex to reverse rocuronium-induced neuromuscular blockade in patients who received 1 mg kg⁻¹ of intraoperative methylprednisolone, demonstrated delayed recovery times.

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* Corresponding author.

E-mail: mervearal@yahoo.com (M.H. Kocaoğlu).

PALAVRAS-CHAVE

Sugammadex;
Rocurônio;
TOF;
Metilprednisolona;
Recuperação

Influência da metilprednisolona no tempo de reversão do sugammadex: estudo clínico randomizado

Resumo

Justificativa e objetivos: Sugammadex é uma gama-ciclodextrina modificada que reverte os efeitos de agentes de bloqueio neuromuscular aminoesteroides. Da mesma forma, algumas moléculas esteroides, como toremifene, ácido fusídico e flucloxacilina, podem ser encapsulados pelo sugammadex. A metilprednisolona, esteroide sintético usado geralmente para a profilaxia de edema de vias aéreas, também pode ser encapsulada pelo sugammadex. O objetivo do estudo foi comparar os tempos de recuperação do sugammadex na reversão de bloqueio neuromuscular moderado induzido pelo rocurônio em pacientes em que foi administrado $1\text{mg}\cdot\text{kg}^{-1}$ de metilprednisolona ou solução salina no período intraoperatório.

Método: Este estudo prospectivo, randomizado, controlado, unicêntrico incluiu 162 pacientes adultos (idades de 18–65, ASA I-II, IMC abaixo de $30\text{kg}\cdot\text{m}^{-2}$, e não usando medicação esteroide) submetidos à anestesia geral para procedimento eletivo de otorrinolaringologia com propofol, remifentanil, rocurônio e sevoflurano. A monitorização neuromuscular foi realizada usando acelerômetro calibrado. O grupo controle (Grupo C) recebeu 5 mL de solução salina, enquanto o grupo metilprednisolona (Grupo M) recebeu $1\text{mg}\cdot\text{kg}^{-1}$ de metilprednisolona em 5 mL de solução salina logo após a indução. Ao término da cirurgia, em relação à contagem do número de respostas à sequência de quatro estímulos (TOFc), dois pacientes mostraram recuperação espontânea e todos os pacientes receberam $2\text{mg}\cdot\text{kg}^{-1}$ de sugammadex. A recuperação da razão T_4/T_1 (TOFr) para 0,9 foi registrada nos dois grupos, e o desfecho primário do estudo foi o tempo estimado de recuperação, momento em que a razão TOFr alcançou o valor de 0,9 (TOFr = 0.9).

Resultados: O tempo mediano para TOFr = 0,9 foi 130 s (29–330) para o Grupo C e 181s (100–420) para o Grupo M ($p < 0,001$). As diferenças entre os dois grupos foi estatisticamente significativa.

Conclusões: Pacientes que receberam $1\text{mg}\cdot\text{kg}^{-1}$ de metilprednisolona no intraoperatório apresentaram tempo de recuperação mais prolongado após o uso de $2\text{mg}\cdot\text{kg}^{-1}$ de sugammadex para reverter o bloqueio neuromuscular induzido pelo rocurônio.

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Introduction

While the use of neuromuscular blocking agents (NMBAs) during surgery optimizes certain surgical conditions, it also carries the risks of residual neuromuscular block and post-extubation respiratory complications.^{1–6} Sugammadex is a modified gamma-cyclodextrin that has been used recently as an alternative to traditional reversal of neuromuscular blockade, which is frequently used in daily anesthetic practice due to its fast and reliable reversal for every degree of neuromuscular blockade.^{7–10} Cyclodextrin molecules with a lipophilic core and hydrophilic outer surface can encapsulate their steroidal target molecules in a 1:1 ratio, which makes them hydro-soluble and facilitates their excretion by urine.^{7,11–13} Sugammadex selectively encapsulates rocuronium and vecuronium and it has a higher specificity to rocuronium.^{14–18}

Methylprednisolone is a synthetic steroid molecule that is frequently used in medical practice as an immunosuppressive agent, and it is also used to prevent airway edema and obstruction after airway instrumentation,¹⁹ Postoperative Nausea and Vomiting (PONV),²⁰ to reduce postoperative pain,²¹ and to treat cerebral edema.^{21–27}

Two types of interactions were reported between sugammadex and other drugs, namely encapsulation and displacement. In a study where the interaction between a plethora of molecules and sugammadex was investigated, it was reported that fusidic acid, toremifene, and flucloxacillin interact by displacing aminosteroid NMBAs from sugammadex and reducing its efficacy.²⁸ Although the route of interaction between sugammadex and oral contraceptives or steroids employs capture, it reduces their plasma concentrations.^{11,18,28,29} The property common to all of these molecules is their steroid structure.

To the best of our knowledge, however, there are no studies in the literature that clinically show the interaction between methylprednisolone and sugammadex. A potential interaction can reduce the effectiveness of both drugs. Decreased plasma methylprednisolone concentrations may lead to an increase in the prevalence of PONV, postoperative pain, and airway reactions after intubation. The reduced effectiveness of sugammadex may prolong the reversal time. We hypothesized that methylprednisolone may interact with sugammadex and extend the reversal time. Thus, the primary objective was to estimate the time necessary to recovery to a Train-Of-Four ratio (TOFr) of 0.9, which is the moment of tracheal extubation.

Method

Study design and patient allocation

This study was approved by the Institutional Review Board of Ankara University (Institutional Ethics Committee Decision N° 16-627-13 on November 11, 2013) and written informed consent obtained from all subjects participating in the trial. The study protocol is registered at clinicaltrials.gov (NCT02025309, date: December 24, 2013) prior to patient enrollment. This study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonization guidelines and current good clinical practices.³⁰ This is a prospective, randomized, controlled, single-centered study. It was conducted with 164 patients who underwent ear-nose-throat procedures in operating rooms at the hospital of Ankara University Faculty of Medicine between December 2013 and May 2014. This study is reported in accordance with the CONSORT Statement.

After obtaining written informed consent, patients scheduled for elective surgery in the ear-nose-throat department aged from 18 to 65, had an ASA score of I–II, a Body-Mass Index (BMI) under 30 kg m^{-2} and had no history of steroid drug intake participated in the study. The exclusion criteria included lack of consent, having diagnosed neuromuscular, liver or renal disease, any kind of arthritic disease that limited their finger range of motion, anticipated difficulty with intubation, pregnancy, nursing, any known allergic reaction to anesthetic drugs used, taking oral contraceptives, and/or taking drugs known to interfere with rocuronium and sugammadex.

Randomization and blinding

Patients were randomly divided into two groups by a computer-generated randomization list and included the Control Group (Group C) and the Methylprednisolone Group (Group M). The allocation sequence was concealed from the researcher responsible for enrolling and assessing participants by using sequentially numbered, opaque and sealed envelopes. A blinded investigator performed all routine and TOF monitoring, drug administrations and data collection and recording. Blinding was assured by pre-filled and unlabeled syringes provided by the hospital pharmacy.

Interventions and neuromuscular monitoring

All patients received 0.5 mg atropine sulfate and 25 mg pethidine HCl i.m. as premedication. Routine monitoring was achieved using ECG, pulse oximetry (SpO_2), capnography, and using non-invasive blood pressure measurement. Anesthesia was induced intravenously with midazolam 0.03 mg kg^{-1} , lidocaine 40 mg, propofol 3 mg kg^{-1} and remifentanyl $1 \mu\text{g kg}^{-1}$. The Control Group (Group C) received i.v. 5 mL saline, and Group M received i.v. methylprednisolone at a dose of 1 mg kg^{-1} in a total volume of 5 mL of saline just after induction.

Neuromuscular monitoring was initiated with an acceleromyograph (TOF-Watch® SX; Organon Ireland Ltd, Dublin, Ireland) to assess the function of the adductor

pollicis muscle after the induction of anesthesia. A piezo-electric probe was attached over the thumb, and two skin electrodes were attached over the ulnar nerve trajectory, which was proximal to the wrist. Stabilization and calibration were performed in compliance with the good clinical research practices in pharmacodynamic studies of NMBAs.³⁰ After induction of anesthesia, TOF stimulation was initiated and reiterated every 15 s for 3 min followed by a 50 Hz 5 s tetanic train. Following this step, automatic calibration (CAL-2 mode) was performed. The TOF-Watch® SX was used to determine the supramaximal current and control twitch height. Subsequently, the device was calibrated. Following stabilization, rocuronium 0.6 mg kg^{-1} was administered, and tracheal intubation was performed after obtaining the adequate neuromuscular block ($\text{TOFc} = 0$). Mechanical ventilation was initiated, and the anesthesia depth was maintained with 1.3 MAC of sevoflurane in a 50% nitrous oxide/oxygen gas mixture throughout the procedure. Intermittent positive-pressure ventilation was established to maintain normocarbida. To sustain adequate neuromuscular block, rocuronium 0.15 mg kg^{-1} was applied when a TOFc of 2 was measured. Repetitive TOF stimulations were applied every 15 s until the T4/T1 ratio recovered to 0.9. For standardized TOF monitoring, the patient's forearm was positioned supine throughout the procedure, and the skin temperature on the wrist was held normothermic, using a forced-air warming system (Bair-Hugger, Arizant Healthcare Inc., USA). Tramadol was administered via i.v. at a dose of 1 mg kg^{-1} for postoperative analgesia.

Outcome measures

After the completion of the surgical procedure, sevoflurane was decreased to an end-tidal concentration of 0.8%–1.0%. As the $\text{TOFc} = 2$ reappeared spontaneously and all patients were administered a single bolus injection of sugammadex at a dose of 2 mg kg^{-1} . Once the TOFc reached 4 and the TOFr recovered to 0.9, the endotracheal tube was removed.

The time to $\text{TOFc} = 0$ after rocuronium administration, the total anesthesia time, the time for TOFc to reach 2 after induction, and the time for TOFr to reach 90% were recorded for both groups.

All neuromuscular data were monitored and compiled throughout the study using a computer. Throughout the procedure, non-invasive arterial blood pressure, heart rate, SpO_2 , respiratory rate, and ETCO_2 were observed, and any adverse effect was also recorded during the surgery and postoperatively for 2 hours.

Sample size and statistical analysis

A priori, power analysis was conducted to determine an appropriate sample size to achieve adequate power. Results of a pilot study with 15 patients from each group showed that groups with a minimum of 78 patients had 80% power, and thus, our study was designed such that each group included at least 82 patients, for a total of 164 patients.

When alpha was 0.05 for the groups with sample sizes of 80 and 82, the mean of the two groups was 131.2, and with the groups' own standard deviations (for $\text{TOFr} = 0.9$; Group

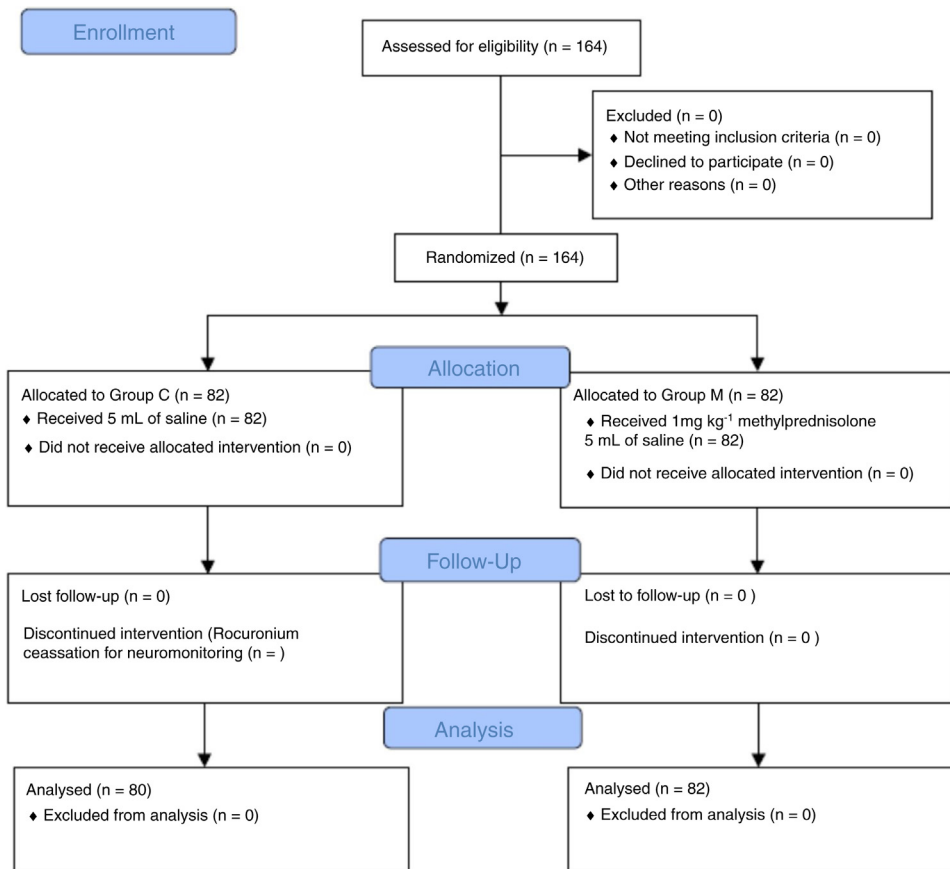


Figure 1 The CONSORT flow diagram of the study.

C, SD = 46.3 and Group M, SD = 54.5), the power analysis calculation revealed a power of approximately 100%.

The obtained data were analyzed using SPSS for Windows version 11.5. The primary objective was to estimate the time needed for TOFr to recover to 0.9.

The variables were investigated using analytical methods (Kolmogorov-Smirnov with Lilliefors Significance Correction) to determine whether they were normally distributed. The Mann-Whitney *U* test was used if the variables had an abnormal distribution. The independent samples *t* test was used to evaluate age and weight and anesthesia time. The χ^2 test was used to evaluate ASA physical status and gender. Categorical measurements (number and percentage) and continuous measurements (mean and SD and, if necessary, median and minimum-maximum) were evaluated. Since TOF measurement, BMI and height values were not normally distributed; this data was evaluated using the Mann-Whitney *U* test. Variance analysis was used to evaluate the repeated measurements. The Mann-Whitney *U* test was used to compare the times to reach a TOFr of 0.9 of the two groups. To evaluate the change in measurements obtained during the time interval, repeated measurement analysis was performed. The level of statistical significance was 0.05 for all tests.

Results

According to the power analysis, a total of 164 patients were eligible for the study and randomized either to the

Control Group (Group C) or the Methylprednisolone Group (Group M). Two patients in Group C were excluded from the study because intraoperative neuromonitoring was considered necessary during thyroid surgery, and muscle relaxation was, thus, interrupted (Fig. 1).

The demographic data of the patients are presented in Table 1. There is no statistically significant difference between groups based on gender, age, height, weight, and BMI ($p > 0.05$).

Anesthesia time measurements showed no statistically significant difference between the two groups ($p = 0.913$). Median time to reach TOFc=0 and to reach TOFc=2 after rocuronium induction were statistically indifferent for Group C and Group M ($p = 0.340$, $p = 0.397$), respectively (Table 2).

The median time recorded from the moment of sugammadex administration to the moment of TOFc=4 and TOFr=0.9 (90%) was 130.00 s for Group C, and 181.00 s for Group M. Mean times were 131.16 s and 192.98 s for groups C and M, respectively. When the groups were compared in terms of the time to TOFr = 0.9, it was statistically significantly longer in the Group M ($p < 0.001$), as shown in Table 3.

Discussion

In this study, the reversal time of sugammadex in patients administered methylprednisolone or saline was evaluated. The results of this study revealed that rocuronium-induced

Table 1 Demographic data of the groups.

	Group C (n = 80)	Group M (n = 82)	p
Gender, n			0.541 ^a
Female	37	40	
Male	43	42	
Age, years	41.38 ± 13.27	40.33 ± 12.62	0.608 ^b
ASA physical status			0.784 ^a
I	63	66	
II	17	16	
Height (cm)	167 (146–183)	170.50 (151–186)	0.051 ^c
Weight (kg)	73.38 ± 11.38	74.88 ± 12.26	0.420 ^b
BMI (kg m ⁻²)	26.00 (16–33)	26.00 (18–36)	0.752 ^c

Age, weight data are reported as mean ± SD, height, BMI data are reported as median (min–max).

BMI, Body Mass Index.

^a χ^2 test;

^b Independent samples *t* test;

^c Mann–Whitney *U* test.

Table 2 Anesthesia, surgery times and duration of time to reach TOFc = 0 and TOFc = 2.

	Group C (n = 80)	Group M (n = 82)	p
Anesthesia time, min ^a	91 ± 12	89 ± 14	0.913 ^c
TOFc = 0, sec ^b	196.50 (57–540)	180.50 (79–589)	0.340 ^d
TOFc = 2, min ^b	43 (20–84)	41 (14–82)	0.397 ^d

TOF, train-of-four; TOFc, train-of-four count.

^a Data reported as mean ± SD.

^b Data are reported as median (min–max).

^c Independent samples *t* test.

^d Mann–Whitney *U* test was used.

Table 3 Time to reach to TOFr: 0.9 after sugammadex administration.

	Group C (n = 80)	Group M (n = 82)	p ^a
TOFr: 0.9 s	130.00 (29–330)	181.00 (100–420)	<0.001

TOF, train-of-four; TOFr, train-of-four ratio.

Data are reported as median (min–max).

^a Mann–Whitney *U* test.

neuromuscular block reversal (time required to reach TOFr = 0.9) using sugammadex is longer when 1 mg kg⁻¹ of methylprednisolone is administered to patients at anesthesia induction. It had been showed that toremifene, fusidic acid, and flucloxacillin displace rocuronium and vecuronium from the sugammadex and impair its efficacy.²⁸ On the other hand, sugammadex interacts with oral contraceptives by means of capture. It is important to note that sugammadex lowers plasma concentrations of hormonal contraceptives when they are found together in plasma. If sugammadex's modus operandi as the encapsulation or displacement of steroidal drugs is considered, our results suggest that there can be a similar interaction between methylprednisolone and sugammadex.

In the literature, an in vitro cell culture study by Rezonja et al. on the interaction between sugammadex and dexamethasone indicated there was a dose-dependent interaction.^{29,31} This study demonstrated that increasing doses of dexamethasone undermined the reversal effect of sugammadex up to 3 fold, in vitro. In another in vitro study by Rezonja et al., the addition of sugammadex to the spinal cord tissue cells in rats and human muscle cells culture, which were exposed to long-term dexamethasone, increased the number of contractions but did not result in a statistically significant difference.³¹ Rezonja et al. also published a study on 60 subjects, which showed no clinical interaction between dexamethasone and 200 mg of sugammadex when the dexamethasone dose was 0.15 mg kg⁻¹.³² Despite the different synthetic steroid molecules considered, our study had a larger sample size and a power that approached 100%.

Buananno et al. demonstrated there was no clinical interaction between dexamethasone and sugammadex in a retrospective study.³³ In a prospective study by Gulec et al. on 60 child patients under general anesthesia, no difference was found between the control and the 0.5 mg kg⁻¹ dexamethasone administered group to reach TOFr = 0.9.³⁴ Although both have a steroid structure, in our study, the use of methylprednisolone may explain the difference.

On the other hand, the interaction between glucocorticoids and NMBAs was revealed.³⁵ As shown by Soltézs et al., dexamethasone decreased the duration of rocuronium induced blockade when it was administered 2–3 h preoperatively.³⁶ However, a recent paper by Geng et al. demonstrated that methylprednisolone (40 mg), no matter preoperatively or intra-operatively, could shorten the duration of rocuronium-induced neuromuscular blockade.³⁷ According to these findings, the effect of rocuronium in our study should have been diminished in the methylprednisolone administered group. On the contrary, our findings indicated that the recovery time was longer in this group. The combinations of these data strengthen the assertion regarding the interaction between sugammadex and methylprednisolone.

In this study, we demonstrated the presence of an interaction between sugammadex and methylprednisolone. While this interaction of 1 mg kg⁻¹ methylprednisolone and 2 mg kg⁻¹ sugammadex was found to be statistically significant in our study, it should be taken into account that when higher doses of methylprednisolone are found in plasma (e.g., unexpected nerve injury, acute brain edema, patients on chronic steroid medication), recovery with sugammadex may be more extensive. As shown in the in vitro study by Rezonja et al., the interaction is dose-dependent.²⁹ Based on this observation, when a higher dose of methylprednisolone is found in the plasma, a prolonged reversal time may be observed. To the best of our knowledge, this study is the first in the literature to investigate the interaction between methylprednisolone and sugammadex in vivo.

Our study has a few limitations. This study lacks a dose-response relationship between methylprednisolone and sugammadex. Secondly, a drawback of our study was the lack of plasma concentration measurements for the two molecules. To investigate the mechanism of action between these molecules, measuring the plasma levels of each drug in blood samples should be included in the scope of future research.

In conclusion, our data suggest that 1 mg kg⁻¹ of methylprednisolone significantly decreases sugammadex's action in a clinical setting. This may also mean that high-dose methylprednisolone therapy during surgery may lead to clinically significant interactions with sugammadex during the reversal of NMB. But it should be noted that both sugammadex and methylprednisolone are frequently-used agents with crucial indications. Thus, even if an interaction is found between these two molecules, they will likely remain in the mainstay of therapy.

Clinical trial registration number

NCT02025309 (<https://clinicaltrials.gov/ct2/show/NCT02025309>).

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Conflicts of interest

The authors declare no conflicts interest.

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