Original Article

Is there an interaction between dexamethasone and sugammadex in real clinical conditions? A randomized controlled trial in patients undergoing laparoscopic cholecystectomy

Chrysanthi Batistaki, Aggeliki Pandazi, Aikaterini Kyttari, Evangelia Kaminiotis, Georgia Kostopanagiotou

2nd Department of Anesthesiology, School of Medicine, National and Kapodistrian University of Athens, "Attikon" Hospital, Athens, Greece

Abstract

Background and Aims: There is evidence that sugammadex can encapsulate other substances except rocuronium, such as dexamethasone. The aim of this study was to investigate the possible clinical interaction between dexamethasone and sugammadex, in patients undergoing laparoscopic cholecystectomy.

Material and Methods: This was a randomized, double-blind controlled trial, performed in patients aged 18–75 years, American Society of Anesthesiologists (ASA) I–III, who underwent a laparoscopic cholecystectomy under deep neuromuscular blockade with rocuronium. Patients received 5 mg of dexamethasone or placebo (N/S 0.9%) during induction of anesthesia. Sugammadex 4 mg/kg was administered at the end of surgery at post-tetanic count 1–2. The outcome measures assessed were the time from sugammadex administration until train-of-four (TOF) 0.9, and until patient's extubation, postoperative pain (measured by numeric rating scale 0–10), nausea and vomiting, as well as rescue analgesics and antiemetics required during the first 24 hours postoperatively. The total dose of rocuronium required in both groups was also recorded.

Results: Overall, 44 patients were studied. No difference was detected regarding the demographic and surgical characteristics of patients. The time from sugammadex administration until TOF 0.9 and until patients' extubation did not differ significantly between the groups ($P = 0.21$ and 0.17). Operating conditions, pain scores, nausea/vomiting, and rescue analgesics and antiemetics during the first 24 hours postoperatively, did not differ between the groups. The total dose of rocuronium, however, was significantly more in patients who received dexamethasone ($P = 0.01$).

Conclusion: No significant clinical interaction was revealed between dexamethasone and sugammadex during reversal of deep neuromuscular blockade in patients undergoing laparoscopic cholecystectomy.

Keywords: Dexamethasone, pain, postoperative, sugammadex

Introduction

Sugammadex is the specific reversal agent of the aminosteroid neuromuscular blocking agents rocuronium and vecuronium, and has been widely used in current clinical practice.[1,2] Sugammadex is a γ-cyclodextrin, designed to encapsulate rocuronium (and vecuronium), leading to the formation of a complex molecule, which is then eliminated through the kidneys.[1-5] However, there is evidence that sugammadex can also encapsulate other substances as well, such as toremiphen, fucidic acid, oral anticontraceptives, steroids, and possibly more.[6]

Address for correspondence: Dr. Chrysanthi Batistaki, 2nd Department of Anesthesiology, School of Medicine, National and Kapodistrian University of Athens, "Attikon" Hospital, Athens, Greece. E-mail: chrysabatistaki@yahoo.gr

Access this article online

Quick Response Code:

Website: www.joacp.org

DOI: 10.4103/joacp.JOACP_42_17

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Batistaki C, Pandazi A, Kyttari A, Kaminiotis E, Kostopanagiotou G. Is there an interaction between dexamethasone and sugammadex in real clinical conditions? A randomized controlled trial in patients undergoing laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol 2019;35:215-9.

Dexamethasone shares the same steroidal ring with rocuronium, leading to a possible encapsulation from sugammadex. Recently, the action of dexamethasone on sugammadex has been investigated *in vitro*[7] as well as *in vivo*,[8,9] but the results were conflicting. *In vitro*, a dose-dependent inhibition of the process of reversal by sugammadex has been observed, in functionally innervated human muscle cells[7] whereas in real clinical conditions, two recent studies have shown no effect.[8,9]

Since dexamethasone is a drug commonly administered perioperatively for its antiemetic and analgesic properties,[10-12] it is very important to assess this possible interaction. In case that dexamethasone is encapsulated by sugammadex, the time of reversal will be prolonged since less sugammadex will be available to reverse rocuronium, and in addition, the efficacy of dexamethasone in nausea, vomiting, and pain will be lessened. Therefore, the aim of this study was to investigate in a prospective, double-blind randomized manner, the possible clinical interaction between dexamethasone and sugammadex, primarily in terms of assessing the time to reverse rocuronium at the end of surgery, and secondarily regarding other actions of dexamethasone, such as antiemetic and analgesic properties in patients undergoing laparoscopic cholecystectomy.

Material and Methods

This study was conducted after approval by the Scientific and Ethics Committee of Attikon University Hospital and if follows the principles of the declaration of Helsinki. All patients included in the study were fully informed about the study protocol and have signed an informed consent. The study has been registered in ClinicalTrials.gov (NCT02510157).

This was a prospective, randomized, double-blind controlled trial that included patients aged 18–75 years, American Society of Anesthesiologists (ASA) classes I–III, who were scheduled for an elective laparoscopic cholecystectomy. Exclusion criteria were as follows: age <18 or >75 years old, ASA > III, duration of >3 hours, operations where a modification of the surgical or the anesthetic plan occurred, psychiatric disorders under systemic treatment, diseases of the central nervous system (i.e., Parkinson's disease, seizures, previous ischemic attack, hydrocephalus, or any other neurological disorder requiring systemic medication), severe cognitive impairment, allergies in any of the drugs used in the study, serious renal disease (creatinine clearance <30 mL/minute) or liver disease, any kind of immunosuppression, diabetes mellitus on insulin therapy, severe endocrine disease, all contraindications of NSAIDs, patients with chronic opioid use, and patients' refusal.

During the pre-anesthetic evaluation, a full medical history was recorded, informed consent was obtained and the patient was allocated by the anesthetist who performed the assessment in one of the two study groups: with or without dexamethasone administration.

The standard anesthetic monitoring was placed before anesthesia (including ECG, SpO_2, blood pressure measurement), in addition to $ETCO_2$, bispectral index (BIS), and a neurostimulator after induction. The neurostimulator (accelerometry device; TOFwatch, Organon, Ireland) was placed at the ulnar nerve of the opposite hand used for intravenous administration of the neuromuscular blocking agent and its antagonist. The study protocol was the same for all patients and included premedication with midazolam (1–2 mg), ranitidine (50 mg), and metoclopramide (10 mg); induction of anesthesia with propofol (2–2.5 mg/kg), fentanyl (3 μg/kg), and rocuronium (1 mg/kg); and maintenance with desflurane (1 MAC), remifentanil and continuous infusion of rocuronium (titrated 0.3–0.6 mg/kg/hour) in order to achieve deep neuromuscular blockade (train-of-four [TOF] 0, post-tetanic count 1–2). The BIS was maintained throughout the operation at a range between 40 and 50 and remifentanil infusion was titrated according to requirements.

Randomization was computer based, and patients were divided in two groups, based on administration or not of dexamethasone 5 mg (1 mg/mL) intravenously or placebo (N/S 0.9% 5 mL) during induction of anesthesia. The syringes where prepared identically, and the anesthesiologist in charge was not aware of the drug to be administered. At the end of surgery, all patients received paracetamol 1 mg, combined to tramadol (1 mg/kg) intravenously, in addition to wound infiltration with ropivacaine 0.375% (20 mL). The rocuronium infusion was maintained until the end of surgery, in order to achieve the same level of deep neuromuscular blockade (PTC 1–2) in all patients before reversal, and in order to administer the same dose of sugammadex. After discontinuation of remifentanil and desflurane, BIS ≥70, the infusion was stopped and sugammadex (4 mg/kg) was administered. Postoperatively, tramadol 1 mg/kg and paracetamol were prescribed every 8 hours.

The primary outcome measure was the time from administration of sugammadex until TOF reached 0.9 (time to reversal) and the time until patient's extubation. Secondary outcomes included pain (assessed by numeric rating scale [NRS] 0–10), nausea and vomiting (measured by the scale proposed by Myles and Wengritzky).[13], and rescue antiemetics and analgesics throughout the first 24 hours postoperatively. Pain and nausea/vomiting [14] were assessed 1 hour after emergence from anesthesia, as well as after 6, 12, and 24 hours. Rescue

drugs administration for pain (parecoxib 40 mg in cases where NRS > 4) and vomiting (ondasentron 4 mg) was also recorded during the follow-up period. The researcher performing the follow-up examination of patients was not aware of the drug that has been administered to the patient. The operating conditions were examined as well, assessed by the surgeon based on a five-item scale (from worse to best operating conditions).[14] The doses of rocuronium and sugammadex were recorded and compared, investigating also possible differences between the two groups.

Statistical analysis

Sample size was calculated based on the pilot study of five patients in each group, according to the primary aim of the study (time from sugammadex administration to TOF 0.9). It was calculated that for 90% power (with alpha error level set at 10% and beta error level of 90%) a number of at least 22 patients per group were required. Categorical measurements are presented as number and percentage, whereas continuous measurements as mean and standard deviation (SD). The χ^2 test or Fisher's exact test, whichever was appropriate, were used to compare the categorical measurements between the two groups, with significance set as $P < 0.05$.

Results

Fifty patients were initially eligible for inclusion. Six patients did not complete the study or were excluded afterward (five due to modification of surgical plan and performance of an open cholecystectomy; one due to inadequate postoperative assessment of outcome measures). In total, 44 patients were, therefore, studied; 22 patients in each group; 28 women and 16 men. Mean age of patients was 52.81 (13.54) years (range 29–75), mean weight 81.5 (16.69) kg, and mean height 168.68 (9.86) cm. Both groups were comparable regarding age, ASA physical status, and somatometric characteristics [Table 1]. No differences were detected regarding the induction dose of rocuronium, neither regarding the dose of sugammadex administered. However, a significant difference was observed regarding the total dose of rocuronium. Patients who received dexamethasone received significantly more rocuronium ($P = 0.01$ [Table 1]).

The time from sugammadex administration at the end of surgery until TOF 0.9 and until patients' extubation did not differ significantly between the two groups ($P = 0.21$ and 0.17, respectively) [Table 2 and Figures 1, 2]. Similarly, operating conditions, pain scores assessed at 1, 6, 12, and 24 hours postoperatively, and nausea and vomiting measured at the same time points, did not differ significantly between the groups [Table 2].

Table 1: Somatometric and demographic characteristics, in addition with surgical data and doses of rocuronium and sugammadex in patients of both groups (Group N/S, *n*=22 and Group dexamethasone, *n*=22)

	Group N/S (*n*=22)	Group dexamethasone (*n*=22)	*P*
Age (years)	52.18 (13.18)	53.45 (13.47)	0.75
Weight (kg)	81.13 (17.11)	81.86 (16.65)	0.88
Height (cm)	168.4 (12.38)	168.95 (6.75)	0.85
Sex (*n*=male/female)	7/15	9/13	0.75
ASA (*n*=I/II/III)	8/13/1	4/18/0	0.16
Duration of operation (min)	72.31 (25.6)	86.86 (26.78)	0.07
Rocuronium dose (mg)	68.86 (12.62)	72.04 (8.26)	0.32
Rocuronium total dose (mg)	81.14 (18.54)	105 (26.54)	0.01
Sugammadex dose (mg)	297.72 (90.69)	327.72 (66.4)	0.21
PTC baseline (before reversal)	1.31 (0.47)	1.4 (0.5)	0.54

Values are expressed as mean (SD). Statistical analysis performed with paired t-test and two-tailed Fisher's exact test. Statistical significance P<0.05. SD=Standard deviation, ASA=American Society of Anesthesiologists, PTC=Post-tetanic count

Table 2: Time from administration of sugammadex until reversal to TOF 0.9 and time to extubation of patients in both groups

	Group N/S (*n*=22)	Group dexamethasone (*n*=22)	*P*
Time to TOF 0.9 (min)	1.92 (1)	2.4 (1.49)	0.21
Time to extubation (min)	2.32 (1.23)	2.91 (1.58)	0.17
Operating conditions	4.54 (0.5)	4.4 (0.5)	0.37
Pain 1 h	3.77 (3.27)	2.9 (2.26)	0.31
Pain 6 h	1.86 (2.21)	1.63 (2.32)	0.74
Pain 12 h	1.4 (1.96)	1.18 (1.76)	0.68
Pain 24 h	1.09 (1.44)	0.86 (1.48)	0.61
Nausea/vomiting 1 h	0.81 (1.5)	0.31 (0.71)	0.16
Nausea/vomiting 6 h	0.18 (0.39)	0.59 (1.25)	0.15
Nausea/vomiting 12 h	0.04 (0.21)	0.27 (0.63)	0.12
Nausea/vomiting 24 h	0.04 (0.21)	0	0.32
Rescue analgesics (*n* doses)	1.04 (0.89)	1.04 (1.25)	1
Rescue antiemetics (*n* doses)	0.13 (0.35)	0.40 (0.85)	0.17

Secondary outcome characteristics (operating conditions assessed by scale 1-5, pain assessed by NRS 0-10, nausea/vomiting score, and number of rescue doses for analgesia and antiemesis) in both groups 1, 6, 12 and 24 h postoperatively (Group N/S, n=22 and Group dexamethasone, n=22). Values are expressed as mean (SD). Statistical analysis performed with paired t-test and two-tailed Fisher's exact test. Statistical significance P<0.05. SD=Standard deviation, TOF=Train-of-four

Discussion

In this study, no significant clinical interaction of dexamethasone with sugammadex's action was observed during reversal of deep neuromuscular blockade, in patients undergoing laparoscopic cholecystectomies. This result is in agreement with other studies investigating this possible interaction, regarding not only time to reverse neuromuscular blockade but also other postoperative factors influenced by dexamethasone, such as pain, nausea, vomiting, as well as analgesics and

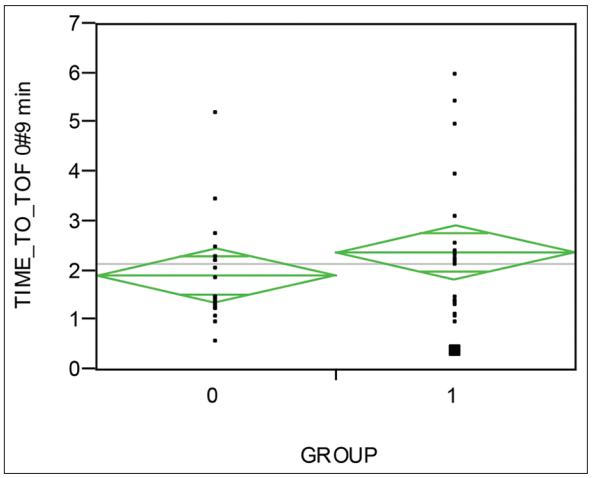

Figure 1: Time (min) from sugammadex administration at post-tetanic count 1–2 to train-of-four 0.9 at the end of surgery in both groups (0 = N/S group, 1 = dexamethasone group)

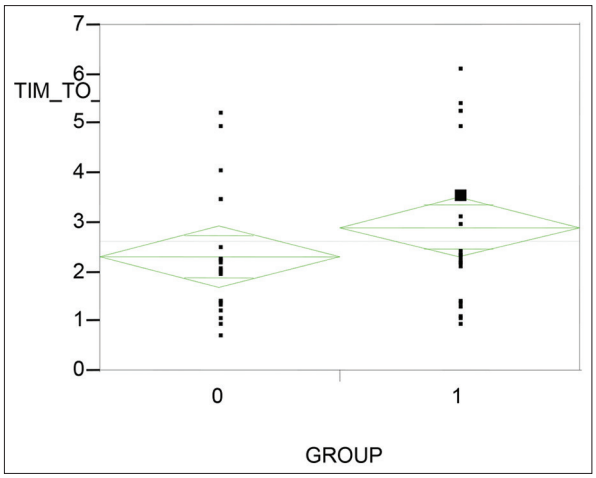

Figure 2: Time (min) from sugammadex administration at post-tetanic count 1–2 until patients' extubation at the end of surgery in both groups (0 = N/S group, 1 = dexamethasone group)

antiemetic requirements. It is of significant clinical interest that no differences were detected in all these factors in such a common clinical setting.

Sugammadex's interaction with other substances is due to its structure (γ-cyclodextrin), which primarily aims to encapsulate the aminosteroid drug and create reversal of the neuromuscular blockade. However, this structure may interact with other similar molecules to rocuronium as well, such as hormonic contraceptives, fucidic acid, flucloxacillin, toremifene, or steroids,[6] leading to decreased availability of sugammadex to act with rocuronium when these substances are also available in plasma. The result of this effect might theoretically be a clinical decrease in sugammadex's action and a delay in the reversal process. Zwiers *et al.*[6] 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.*,[7] in innervated human muscle cells, showed that there was a dose-dependent inhibition of sugammadex's action by dexamethasone. Therefore, the necessity of clinical trials to assess this effect in real anesthetic practice conditions was obvious.

The two clinical studies performed so far, in addition to our results, failed to prove a clinically significant interaction of dexamethasone with sugammadex. Buonanno *et al.*[8] 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 (of 15 patients each), 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. Similarly, Gulec *et al.*[9] 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. All patients received sugammadex at the end of surgery, at a dose of 2 mg/kg at reappearance of T2. No significant difference was also observed regarding the time required from administration of sugammadex until reversal of neuromuscular function to TOF 0.9 between the two groups.

This clinical observation, reported by these two studies and from our results, is also supported by Zwiers *et al.*,[6] who demonstrated that the binding affinity of rocuronium with sugammadex is very high, and therefore, clinical interaction with other substances might be unlikely in real clinical conditions. Since dexamethasone is a commonly administered drug perioperatively, due to its antiemetic and analgesic properties, it is of great importance to exclude this clinical interaction with sugammadex, when both of them are used in clinically accepted doses. The most common timing of dexamethasone's administration is at the beginning of surgery that is before the surgical incision, usually as a single bolus. However, due to the long elimination half time of the drug, it is still in action during administration of sugammadex in most clinical conditions (such as the laparoscopic cholecystectomies or the adeno-tonsillectomies in children). It is not known so far, what the effect would be if the two drugs are administered simultaneously, or in different doses, but this is not clinically common.

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 study of Soltész *et al*.,[15] demonstrated that a single bolus dose of dexamethasone (8 mg) when administered 2–3 hours prior surgery shortened the duration of rocuronium-induced neuromuscular blockade by nearly 15%–20%, without affecting onset time. 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.[15] Other mechanisms may interact as well, but this is yet to be defined.

Our study has a number of limitations. We did not have concentration measurements of dexamethasone, and all patients received the same dose at induction of anesthesia, leading to possible bias. However, we used a standardized dose, commonly accepted for clinical use in laparoscopic cholecystectomies and aimed on mirroring real clinical conditions, using deep neuromuscular blockade and strict monitoring in order to provide accuracy of measurements. The use of deep neuromuscular blockade was selected in order to reverse all patients from exactly the same depth of neuromuscular blockade with the same dose of sugammadex, an action that could not be performed using medium neuromuscular blockade, due to variable TOF count at the end of surgery. In this study, deep blockade was maintained until the time of reversal, a fact that made measurement of time more precise. In addition, deep blockade is commonly used in laparoscopic operations, since it is associated with less pain postoperatively and better surgical conditions.

Conclusions

This study did not show a clinical interaction between dexamethasone and sugammadex during reversal of deep neuromuscular blockade, in patients undergoing laparoscopic cholecystectomies. Further research is required, using different doses of dexamethasone and different time points of administration to further evaluate this result.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Kopman AF. Neuromuscular monitoring: Old issues, new controversies. J Crit Care 2009;24:11-20.
2. Fink H, Hollmann MW. Myths and facts in neuromuscular pharmacology. New developments in reversing neuromuscular blockade. Minerva Anestesiol 2012;78:473-82.
3. Schaller SJ, Fink H. Sugammadex as a reversal agent for neuromuscular block: An evidence-based review. Core Evid 2013;8:57-67.
4. Schaller S, Fink H. A randomized controlled trial comparing sugammadex and neostigmine at different depths of neuromuscular blockade in patients undergoing laparsoscopic surgery. Anaesthesia 2012;67:991-8.
5. Plaud B, Meretoja O, Hofmockel R, Raft J, Stoddart PA, van Kuijk JH, *et al.* Reversal of rocuronium-induced neuromuscular blockade with sugammadex in pediatric and adult surgical patients. Anesthesiology 2009;110:284-94.
6. Zwiers A, van den Heuvel M, Smeets J, Rutherford S. Assessment of the potential for displacement interactions with sugammadex: A pharmacokinetic-pharmacodynamic modelling approach. Clin Drug Investig 2011;31:101-11.
7. Rezonja K, Sostaric M, Vidmar G, Mars T. Dexamethasone produces dose-dependent inhibition of sugammadex reversal in *in vitro* innervated primary human muscle cells. Anesth Analg 2014;118:755-63.
8. Buonanno P, Laiola A, Palumbo C, Spinelli G, Servillo G, Minno RM, *et al*. Dexamethasone dose not inhibit sugammadex reversal after rocuronium-induced neuromuscular block. Anesth Analg 206;122:1826-30.
9. Gulec E, Biricik E, Turktan M, Hatipoglu Z, Unlugenc H. The effect of intravenous dexamethasone on sugammadex reversal time in children undergoing adenotonsillectomy. Anesth Analg 2016;122:1147-52.
10. Bernardo WM, Aires FT. Efficacy of dexamethasone in the prophylaxis of nausea and vomiting during the postoperative period of laparoscopic cholecystectomy. Rev Assoc Med Bras (1992) 2013;59:387-91.
11. De Oliveira GS Jr, Castro-Alves LJ, Ahmad S, Kendall MC, McCarthy RJ. Dexamethasone to prevent postoperative nausea and vomiting: An updated meta-analysis of randomized controlled trials. Anesth Analg 2013;116:58-74.
12. Waldron NH, Jones CA, Gan TJ, Allen TK, Habib AS. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: Systematic review and meta-analysis. Br J Anaesth 2013;110:191-200.
13. Myles PS, Wengritzky R. Simplified postoperative nausea and vomiting impact scale for audit and post-discharge review. Br J Anaesth 2012;108:423-9.
14. Martini CH, Boon M, Bevers RF, Aarts LP, Dahan A. Evaluation of surgical conditions during laparoscopic surgery in patients with moderate vs. Deep neuromuscular block. Br J Anaesth 2014;112:498-505.
15. Soltész S, Fraisl P, Noé KG, Hinkelbein J, Mellinghoff H, Mencke T, *et al.* Dexamethasone decreases the duration of rocuronium-induced neuromuscular block: A randomised controlled study. Eur J Anaesthesiol 2014;31:417-22.