KJA
Korean Journal of Anesthesiology

Experimental Research Article
pISSN 2005-6419 • eISSN 2005-7563

The effect of magnesium sulfate concentration on the effective concentration of rocuronium, and sugammadex-mediated reversal, in isolated left phrenic nerve hemi-diaphragm preparations from the rat

Choon-kyu Cho[1], Tae-yun Sung[1], Seok-Jun Choi[1], Hey-ran Choi[2], Yong Beom Kim[3], Jung-Un Lee[4], and Hong-Seuk Yang[5]

Department of Anesthesiology and Pain Medicine, [1]Konyang University Hospital, Konyang University College of Medicine, Daejeon, [2]Seoul Paik Hospital, Inje University College of Medicine, Seoul, [3]Gachon University Gil Medical Center, Incheon, [4]Chungnam National University Hospital, Daejeon, [5]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background: Perioperative magnesium sulfate ($MgSO_4$) is used for analgesic, anti-arrhythmic, and obstetric purposes. The effects of $MgSO_4$ on the neuromuscular blockade (NMB) induced by rocuronium, and the sugammadex reversal thereof, have not been clearly quantified. We investigated the effect of various $MgSO_4$ concentrations on the NMB by rocuronium, and sugammadex reversal, in isolated left phrenic nerve hemi-diaphragm (PNHD) preparations from the rat.
Methods: Rat PNHD preparations were randomly allocated to one of four groups varying in terms of $MgSO_4$ concentration (1, 2, 3, and 4 mM, each n = 10, in Krebs solution). The train-of-four (TOF) and twitch height responses were recorded mechanomyographically. The preparations were treated with incrementally increasing doses of rocuronium and each group's effective concentration $(EC)_{50}$, EC_{90}, and EC_{95} of rocuronium were calculated via nonlinear regression. Then, sugammadex was administered in doses equimolar to rocuronium. The recovery index, time to T1 height > 95% of control, and the time to a TOF ratio > 0.9 after sugammadex administration were measured.
Results: The EC_{50}, EC_{90}, and EC_{95} of rocuronium fell significantly as the magnesium level increased. The EC_{50}, EC_{90}, and EC_{95} of rocuronium did not differ between the 3 and 4 mM groups. The recovery index, time to T1 height > 95% of control, and time to a TOF ratio > 0.9 after sugammadex administration did not differ among the four groups.
Conclusions: Increases in the magnesium concentration in rat PNHD preparations proportionally enhanced the NMB induced by rocuronium but did not affect reversal by equimolar amounts of sugammadex.

Keywords: Adverse effects; Anesthesia; Magnesium sulfate; Neuromuscular blockade; Rocuronium; Sugammadex.

Corresponding author: Hong-Seuk Yang, M.D., Ph.D.
Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Sonpa-gu, Seoul 05505, Korea
Tel: 82-2-3010-5245, Fax: 82-2-470-1363, Email: hsyang@amc.seoul.kr
ORCID: https://orcid.org/0000-0003-2023-8705

Received: June 19, 2017. Revised: September 26, 2017 (1st); December 31, 2017 (2nd); February 8, 2018 (3rd). Accepted: February 19, 2018.

Korean J Anesthesiol 2018 October 71(5): 401-406
https://doi.org/10.4097/kja.d.17.27150

Introduction

Magnesium is mainly used to treat pregnancy-induced hypertension, usually in the form of magnesium sulfate ($MgSO_4$) [1]. The use of magnesium to treat acute myocardial infarction, asthma, arrhythmia, and pheochromocytoma; and to induce postoperative analgesia; is increasing [2]. Despite the fact that magnesium is relatively safe hemodynamically [2,3], magnesium use is associated with serious complications in terms of neuromuscular blockade (NMB), including respiratory arrest [4]. Magnesium enhances the action of nondepolarizing neuromuscular blocking agents (NMBAs) [5]. The effective dose $(ED)_{50}$ of pipecuronium changed in inverse proportion to the increase in magnesium concentration in animal studies [6]. Magnesium shortened the time to NMB onset mediated by rocuronium at an effective concentration (EC) of effective concentration $(EC)_{95}$ [7]. In addition, magnesium prolonged the duration of action of rocuronium [8,9]. A study using isolated phrenic nerve diaphragm preparations from the mouse found that a higher dose of sugammadex was required to reverse rocuronium-induced NMB when the magnesium concentration was increased from 3.50 to 4.07 mM [10]. Recurarization can occur when magnesium is added after sugammadex reversal [11], but recurarization was reduced when the sugammadex dose was increased [10]. Previous studies led us to expect that the rocuronium effect would increase and the sugammadex-mediated reversal effect would decrease when magnesium was administered [8–10]. However, it remained unclear whether these effects would change in proportion to the magnesium concentration.

The normal level of magnesium in the human body is 0.7–1.1 mM and the therapeutic concentration used to treat pre-eclampsia is 2–4 mM [1]. The patellar reflex is inhibited by 3.5–5 mM magnesium and respiratory paralysis develops at magnesium levels greater than 6 mM [4]. In pre-eclampsia patients, the methods used to monitor the side-effects of magnesium therapy include measurement of blood magnesium concentration, the patellar reflex, and various clinical features [12].

We planned the present study to explore whether increased concentrations of $MgSO_4$, from the reference level (1 mM), which is normal in the human body to 2, 3, and 4 mM, proportionally enhanced NMB caused by rocuronium and hindered sugammadex-induced NMB reversal.

Materials and Methods

After approval was granted by Asan hospital Institutional Review Board for Animal Studies (no. 2016-13-067), 40 male Sprague-Dawley rats (219 [13] g, 43 [6] days of age) were randomly allocated to four groups with different magnesium concentrations (1, 2, 3, and 4 mM, each n = 10). The rats were anesthetized with 30 mg/kg intraperitoneal Zoletil® (Virbac®, France) and euthanized. The thoracic cages were excised en bloc and isolated left phrenic nerve hemi-diaphragms prepared. Each specimen was placed in a 75 ml organ bath containing Krebs buffer solution (pH 7.4: NaCl 118 mM, KCl 5.0 mM, $CaCl_2$ 2.5 mM, $NaHCO_3$ 30 mM, KH_2PO_4 1.0 mM, $MgSO_4$ 1.0 mM, and glucose 11.4 mM) [13]. The bath was held at 35°C via outer warm water circulation and 95% oxygen and 5% carbon dioxide were continuously bubbled into the Krebs solution. The train-of-four (TOF) and twitch height responses were recorded mechanomyographically. The rib of each specimen was fixed to point downward, and the tendinous portion upward; the specimen was connected to a force displacement transducer® (Grass FT03®, Grass Instruments®, USA) and preloaded to 2 g. A bipolar platinum electrode was connected to the phrenic nerve and stimulated with TOF pulses (2 Hz supramaximal stimulation) 0.2 ms in length (pulse duration) using a Grass S88 stimulator® and an SIU5 stimulus isolation unit® (Grass Instruments®, USA). TOF stimulation was continued at intervals of 20 s until the end of the study. Muscle contraction was measured using the force displacement transducer and digitalized with the aid of the Powerlab® acquisition system (Millar®, USA). All signals were digitally saved using charting software (Lab Chart®, ADinstruments®, USA). After 30 min of stabilization, the magnesium concentrations were set to 2, 3, or 4 mM using $MgSO_4$ in the 2, 3, and 4 mM groups. $MgSO_4$ was not added to the 1 mM group because the magnesium concentration of the Krebs solution was 1 mM. After additional stabilization over 20 min, the T1 and train-of-four ratio (TOFR) after $MgSO_4$ administration were compared to the pre-administration values within each group. Then, the first dose of rocuronium (200 μg) was added to the organ bath. The T1 heights just before administration of rocuronium were considered the control values for each group. The rocuronium dose was increased in 100 μg increments until T1 height was completely suppressed in each group. Prior to every addition of rocuronium, we waited for 10 min or observed similar T1 height responses on at least three consecutive measurements. We then calculated the EC_{50}, EC_{90}, and EC_{95} of each group.

Ten minutes after the T1 height was completely suppressed, equimolar doses of sugammadex (3.57-fold the total weight [mg] of rocuronium added) were in turn added. T1 height and TOFR recovery were observed for 30 min after administration of sugammadex; and we measured the following variables: maximum T1 height; the recovery index (the time to recovery from 25% to 75% of the control value of T1 height); the time taken for T1 height to attain 95% of the control T1 height (the 95% T1 time); the time taken for the TOFR to attain 0.9 (the TOFR 0.9 time); and the number of samples that failed to attain TOFR 0.9 and 95% of the control T1 height in each group.

Statistical analysis

Values are expressed as mean (SD). The primary outcome variable was time after sugammadex injection to TOFR 0.9. To determine the required sample size, we measured the time from sugammadex administration to TOFR 0.9 in four groups (1, 2, 3, and 4 mM $MgSO_4$ in the organ bath, each n = 3) in a pilot study. The times for the four groups were 17.8 (3.1), 20.2 (4.5), 18.9 (3.0), and 21.3 (2.9) min (1, 2, 3, and 4 mM $MgSO_4$, respectively). The effect size f calculated using Cohen's formula was 0.6. R (a language and environment for statistical computing, ver. 3.4.1, R Foundation for Statistical Computing, Austria. Available from https://www.R-project.org.) indicated that nine specimens in each group would afford an $\alpha = 0.05$, a power = 0.8, and an f = 0.6. We used 10 specimens in each group to allow for dropout.

The normalities of continuous variables were assessed using the Shapiro-Wilk test. T1 and TOFR changes before and after addition of $MgSO_4$ in each group were compared using the paired *t*-test. Differences in the dose of the rocuronium administered, ECs, maximum T1 height, recovery indices, 95% T1 times, and TOFR 0.9 times among the groups were assessed using analysis of variance, followed by the Bonferroni correction for multiple pairwise comparisons. The number of samples with T1 height < 95% of control and in which the TOFR did not attain 0.9 were compared using the χ^2-test for trend. The ECs of rocuronium were calculated via nonlinear regression analysis; thus using the four-parameter logistic curve equation of the Sigma Plot® program (ver. 12.5 for Windows, Systat Software, USA). All statistical analyses were conducted with the aid of SPSS® software (ver. 18.0, SPSS Inc., USA). P values < 0.05 were regarded as statistically significant.

Results

For thirty minutes of initial stabilization in each group when the magnesium level was not increased, the T1 height and TOFR did not differ among the groups. However, after $MgSO_4$ administration and an additional 20 min of stabilization, T1 height exhibited significant decline in the 2, 3, and 4 mM magnesium groups (P = 0.002, 0.001, and < 0.001 respectively), but the TOFR did not (Table 1). As the concentration of $MgSO_4$ increased, the EC_{50}, EC_{90}, and EC95 significantly decreased (all groups P < 0.001), but pairwise comparisons showed no difference between the 3 and 4 mM magnesium groups (Table 2).

The primary outcome, the TOFR 0.9 time, did not differ among the groups after bolus sugammadex administration. T1 height recovery (maximum T1 height, recovery index, and the 95% T1 time), and the number of samples that failed to reach TOFR 0.9 or T1 height 95% of control did not differ among the groups after bolus sugammadex administration (Table 3).

Discussion

In this study, TOFR 0.9 times after equimolar sugammadex administration were not affected by an increase in magnesium concentration. However, we recorded T1 height depression but no TOFR depression in the 2, 3, and 4 mM $MgSO_4$ groups compared to before magnesium addition. In addition, the EC_{50}, EC_{90}, and EC_{95} decreased as the magnesium concentration increased from 1 to 4 mM, but we found no statistically significant change between 3 and 4 mM $MgSO_4$.

Magnesium induces NMB by reducing prejunctional acetylcholine (Ach) release, decreasing the excitability of the junction-

Table 1. T1 Height (T1) and TOFR Changes after Addition of $MgSO_4$ to Each Group

	1 mM (n = 10)	2 mM (n = 10)	3 mM (n = 10)	4 mM (n = 10)
T1 (stabilization, 1 mM)	15.4 (4.1)	13.1 (2.2)	13.8 (3.2)	14.0 (3.7)
T1 ($MgSO_4$ added)	15.1 (4.0)	12.2 (2.0)*	13.0 (2.9)*	12.5 (3.3)*
TOFR (stabilization, 1 mM)	0.99 (0.02)	0.99 (0.01)	1.00 (0.01)	1.00 (0.02)
TOFR ($MgSO_4$ added)	0.99 (0.02)	1.00 (0.01)	1.00 (0.01)	1.00 (0.01)

Values are expressed as mean (SD). T1: T1 height of train-of-four, TOFR: train-of-four ratio. *P < 0.05 compared to T1 height before addition of magnesium sulfate within group.

Table 2. The Doses of Rocuronium and Effective Concentration $(EC)_{50}$, EC_{90}, and EC_{95} Values of Rocuronium in Each Group

	1 mM (n = 10)	2 mM (n = 10)	3 mM (n = 10)	4 mM (n = 10)	P value
Rocuronium (μg)	1,020.0 (103.3)†	750.0 (108.0)*	590.0 (56.8)*,†	580.0 (63.2)*,†	< 0.001
EC_{50} (μg/ml)	8.5 (1.1)	6.1 (1.2)*	4.7 (0.4)*,†	4.4 (0.8)*,†	< 0.001
EC_{90} (μg/ml)	11.9 (1.3)	8.7 (1.4)*	6.8 (0.7)*,†	6.4 (0.9)*,†	< 0.001
EC_{95} (μg/ml)	12.7 (1.3)	9.3 (1.4)*	7.4 (0.9)*,†	6.9 (0.9)*,†	< 0.001

Values are expressed as mean (SD). EC: effective concentration. *P < 0.05 compared to the 1 mM magnesium sulfate group, and †P < 0.05 compared to the 2 mM magnesium sulfate group.

Table 3. The Recovery Profile of Each Group

	1 mM (n = 10)	2 mM (n = 10)	3 mM (n = 10)	4 mM (n = 10)	P value
Maximum T1 (%)	89.5 (12.5)	97.7 (11.0)	98.8 (7.1)	100.1 (7.2)	0.081
Recovery index (min)	7.8 (6.8)	6.2 (3.7)	5.5 (1.8)	6.8 (2.7)	0.653
T1 95% time (min)	10.7 (4.4)	9.7 (2.6)	12.3 (3.9)	13.8 (2.7)	0.103
TOFR 0.9 time (min)	15.2 (4.5)	16.2 (6.7)	16.2 (6.3)	21.2 (5.9)	0.122
No. of T1 < 95%	5	4	3	2	0.143
No. of TOFR < 0.9	1	0	0	0	0.180

Values are expressed as mean (SD) or number. TOFR: train-of-four ratio, T1: T1 height of train-of-four, Recovery index: time to recovery from 25% to 75% of the control value of T1 height, T1 95% time: time from sugammadex administration to the time when T1 height attained 95% of the control value, TOFR 0.9 time: time from sugammadex administration to the time when the TOFR attained 0.9, No. of T1 < 95%: number of cases in which T1 height did not attain 95% of control, and No. of TOFR < 0.9: number of cases in which TOFR did not attain 0.9.

al nicotinic Ach receptor (nAchR) and the muscle membrane. Magnesium acts principally at the prejunctional membrane by competitively antagonizing calcium influx [14]. As magnesium reduces all four of the twitch heights of the TOF, magnesium has only a minor effect on TOF fading [15]. Therefore, magnesium causes T1 height depression, but not any significant change in the TOFR.

The effect of magnesium are dependent on its concentration [14,16]; NMB is enhanced when NMBAs are concurrently administered. When the magnesium concentration increased from 1 to 3 mM, the EC_{50}, EC_{90}, and EC_{95} of rocuronium decreased by about 22–28% for each 1 mM increase (Table 2). In a pipecuronium study, when the magnesium concentration was increased to 1.2, 2, 2.75, and 3.5 mM, the ED_{50} of pipecuronium continuously fell, but no change was found between 2 and 2.75 mM in the rat [6]. The atracurium requirement was not reduced, even though the magnesium infusion rate was increased during total intravenous anesthesia with propofol, in humans [17]. It is unclear whether magnesium concentrations within a certain range may exhibit a ceiling-like interaction with rocuronium and other nondepolarizing NMBAs [6,17]. Further study is needed.

Sugammadex effectively reverses rocuronium-induced NMB in patients undergoing magnesium therapy [15]. Elevated magnesium concentrations increase the levels of sugammadex required for reversal, and recurarization after injection of magnesium was reduced when the sugammadex dose was increased [10]. Therefore, we expected that addition of equimolar doses of sugammadex to baths that had received rocuronium in the presence of different concentrations of magnesium might be associated with different extents of recovery. However, neither the T1 height nor TOFR recovery differed among groups after equimolar doses of sugammadex were added. At the TOFR 0.9, 70% of postsynaptic receptors were still occupied by NMBAs [18,19]. This phenomenon may explain NMB recurrence after the administration of NMB-promoting agents such as magnesium [20]. Recurarization after magnesium administration may reflect insufficient dosing by sugammadex and residual NMBA. Rocuronium was completely removed in the present study because no pharmacokinetic variation was evident in the organ bath tests. Thus, changes in magnesium concentration (from 1 to 4 mM) did not seem to affect recovery mediated by sugammadex. This result is consistent with that of a rabbit study in which sugammadex at doses of more than 4 mg/kg was associated with similar recoveries among magnesium-infused and non-infused groups of rabbits [21]. It is likely that the dose of sugammadex is more important than the magnesium concentration in terms of clinically acceptable limits; neuromuscular transmission monitoring is essential to ensure that sufficient sugammadex is administered.

A TOFR of 0.9 is considered safe in terms of extubation and recovery [22]; we used the TOFR 0.9 time as the primary outcome. The primary outcome, the TOFR 0.9 time, did not differ among the groups after bolus sugammadex administration. In an earlier study of sugammadex reversal, a lower dose of sugammadex (≤ 4 mg/kg) after NMB induced by rocuronium of 1.2 mg/kg allowed recovery of T1 height faster than TOFR that is also similarly seen during spontaneous recovery and cholinesterase reversal, but the opposite result was reported when high-dose sugammadex (> 8 mg/kg) was given [23]. We suspect that small amounts of free NMBAs not removed by sugammadex may have a greater affinity for postsynaptic nAchR than presynaptic nAchR early in the recovery period [24,25]. Thus, TOFR recovery may precede T1 height recovery in the early recovery period. Sufficient T1 recovery follows within minutes. A previous study also posed the question of whether this feature of sugammadex reversal was unchanged in the presence of medication that affects nAchR such as magnesium or an aminoglycoside [23]. T1 height recovery (the T1 95% time) was faster than TOFR recovery (the TOFR 0.9 time) in the present study (Table 3). This suggests that an equimolar dose of sugammadex may recover T1 height earlier than TOFR when a rocuronium-induced NMB is in play in the presence of magnesium.

A limitation of this study is that the recovery conditions were not identical among the groups. The rocuronium dose was the

highest and the time available for observation prior to sugammadex administration the longest in the 1 mM magnesium group than the other groups. This may affect the recovery results. A further study may be needed to more accurately evaluate the effect of magnesium concentration on the required sugammadex level. With the presence of different concentrations of $MgSO_4$, the addition of increments of sugammadex followed by single-bolus administration of rocuronium would be useful to observe recovery. The second limitation is that half of the 1 mM group failed to reach T1 height 95% that of the control. Even though it is not statistically significant, some experimental errors may have occurred.

In conclusion, increases in the $MgSO_4$ concentration in isolated phrenic nerve hemi-diaphragmatic preparations from the rat did not affect TOFR recovery after addition of equimolar doses of sugammadex, but the NMB induced by rocuronium was enhanced in proportion to the magnesium concentration from 1 to 3 mM.

ORCID

Choon-kyu Cho, https://orcid.org/0000-0002-3960-2514
Tae-yun Sung, https://orcid.org/0000-0002-0714-1477
Seok-Jun Choi, https://orcid.org/0000-0003-0202-1369
Hey-ran Choi, https://orcid.org/0000-0002-9899-0158
Yong Beom Kim, https://orcid.org/0000-0003-2369-6525
Hong-Seuk Yang, https://orcid.org/0000-0003-2023-8705

References

1. Pritchard JA, Cunningham FG, Pritchard SA. The Parkland Memorial Hospital protocol for treatment of eclampsia: evaluation of 245 cases. Am J Obstet Gynecol 1984; 148: 951-63.
2. James MF. Magnesium: an emerging drug in anaesthesia. Br J Anaesth 2009; 103: 465-7.
3. Nakayama T, Nakayama H, Miyamoto M, Hamlin RL. Hemodynamic and electrocardiographic effects of magnesium sulfate in healthy dogs. J Vet Intern Med 1999; 13: 485-90.
4. Winkler AW, Smith PK, Hoff HE. Intravenous magnesium sulfate in the treatment of nephritic convulsions in adults. J Clin Invest 1942; 21: 207-16.
5. Yoshida A, Itoh Y, Nagaya K, Takino K, Sugawara J, Murakami T, et al. Prolonged relaxant effects of vecuronium in patients with deliberate hypermagnesemia: time for caution in cesarean section. J Anesth 2006; 20: 33-5.
6. Kim JS, Ryu TG, Kong MH, Lee MK, Yoon SM. The effects of magnesium on pipecuronium-induced neuromuscular blockade and its reversal in the isolated rat phrenic nerve-hemidiaphragm. Korean J Anesthesiol 1996; 31: 150-5.
7. Koo EH, Yoon SM, Hwang KH, Kim SY. The effect of sium on the onset time of rocuronium-induced neuromuscular blockade in the isolated rat phrenic nerve-hemidiaphragm. Korean J Anesthesiol 1999; 37: 467-71.
8. Czarnetzki C, Lysakowski C, Elia N, Tramèr MR. Time course of rocuronium-induced neuromuscular block after pre-treatment with magnesium sulphate: a randomised study. Acta Anaesthesiol Scand 2010; 54: 299-306.
9. Kussman B, Shorten G, Uppington J, Comunale ME. Administration of magnesium sulphate before rocuronium: effects on speed of onset and duration of neuromuscular block. Br J Anaesth 1997; 79: 122-4.
10. Bom A, Hope F, Rutherford S, Thomson K. Preclinical pharmacology of sugammadex. J Crit Care 2009; 24: 29-35.
11. Unterbuchner C, Ziegleder R, Graf B, Metterlein T. Magnesium-induced recurarisation after reversal of rocuronium-induced neuromuscular block with sugammadex. Acta Anaesthesiol Scand 2015; 59: 536-40.
12. Lu JF, Nightingale CH. Magnesium sulfate in eclampsia and pre-eclampsia: pharmacokinetic principles. Clin Pharmacokinet 2000; 38: 305-14.
13. Lee YK, Park SK, Kim JW, Yang HS, Han SM. Effects of phenytoin on rocuronium-induced neuromuscular blockade using a rat phrenic nerve-diaphragm preparation. Korean J Anesthesiol 2003; 45: 244-50.
14. Jenkinson DH. The nature of the antagonism between calcium and magnesium ions at the neuromuscular junction. J Physiol 1957; 138: 434-44.
15. Czarnetzki C, Tassonyi E, Lysakowski C, Elia N, Tramèr MR. Efficacy of sugammadex for the reversal of moderate and deep rocuronium-induced neuromuscular block in patients pretreated with intravenous magnesium: a randomized controlled trial. Anesthesiology 2014; 121: 59-67.
16. Wang H, Liang QS, Cheng LR, Li XH, Fu W, Dai WT, et al. Magnesium sulfate enhances non-depolarizing muscle relaxant vecuronium action at adult muscle-type nicotinic acetylcholine receptor in vitro. Acta Pharmacol Sin 2011; 32: 1454-9.
17. Seyhan TO, Tugrul M, Sungur MO, Kayacan S, Telci L, Pembeci K, et al. Effects of three different dose regimens of magnesium on propofol requirements, haemodynamic variables and postoperative pain relief in gynaecological surgery. Br J Anaesth 2006; 96: 247-52.
18. Paton WD, Waud DR. The margin of safety of neuromuscular transmission. J Physiol 1967; 191: 59-90.
19. Waud BE, Waud DR. The relation between the response to "train-of-four" stimulation and receptor occlusion during competitive neuromuscular block. Anesthesiology 1972; 37: 413-6.

20. Hans GA, Bosenge B, Bonhomme VL, Brichant JF, Venneman IM, Hans PC. Intravenous magnesium re-establishes neuromuscular block after spontaneous recovery from an intubating dose of rocuronium: a randomised controlled trial. Eur J Anaesthesiol 2012; 29: 95-9.
21. Kang WS, Kim KS, Song SM. Reversal with sugammadex for rocuronium-induced deep neuromuscular block after pretreatment of magnesium sulfate in rabbits. Korean J Anesthesiol 2017; 70: 203-8.
22. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS, et al. Intraoperative acceleromyographic monitoring reduces the risk of residual neuromuscular blockade and adverse respiratory events in the postanesthesia care unit. Anesthesiology 2008; 109: 389-98.
23. Abad-Gurumeta A, Ripollés-Melchor J, Casans-Francés R, Espinosa A, Martínez-Hurtado E, Fernández-Pérez C, et al. A systematic review of sugammadex vs neostigmine for reversal of neuromuscular blockade. Anaesthesia 2015; 70: 1441-52.
24. Staals LM, Driessen JJ, Van Egmond J, De Boer HD, Klimek M, Flockton EA, et al. Train-of-four ratio recovery often precedes twitch recovery when neuromuscular block is reversed by sugammadex. Acta Anaesthesiol Scand 2011; 55: 700-7.
25. Jonsson M, Gurley D, Dabrowski M, Larsson O, Johnson EC, Eriksson LI. Distinct pharmacologic properties of neuromuscular blocking agents on human neuronal nicotinic acetylcholine receptors: a possible explanation for the train-of-four fade. Anesthesiology 2006; 105: 521-33.