

Efficacy of Sugammadex for the Reversal of Moderate and Deep Rocuronium-induced Neuromuscular Block in Patients Pretreated with Intravenous Magnesium

A Randomized Controlled Trial

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ABSTRACT

Background: Magnesium enhances the effect of rocuronium. Sugammadex reverses rocuronium-induced neuromuscular block. The authors investigated whether magnesium decreased the efficacy of sugammadex for the reversal of rocuronium-induced neuromuscular block.

Methods: Thirty-two male patients were randomized in a double-blinded manner to receive magnesium sulfate (MgSO_4) 60 mg/kg or placebo intravenously before induction of anesthesia with propofol, sufentanil, and rocuronium 0.6 mg/kg. Neuromuscular transmission was monitored using TOF-Watch SX[®] acceleromyography (Organon Ltd., Dublin, Ireland). In 16 patients, sugammadex 2 mg/kg was administered intravenously at reappearance of the second twitch of the train-of-four (moderate block). In 16 further patients, sugammadex 4 mg/kg was administered intravenously at posttetanic count 1 to 2 (deep block). Primary endpoint was recovery time from injection of sugammadex to normalized train-of-four ratio 0.9. Secondary endpoint was recovery time to final T1.

Results: Average time for reversal of moderate block was 1.69 min (SD, 0.81) in patients pretreated with MgSO_4 and 1.76 min (1.13) in those pretreated with placebo ($P = 0.897$). Average time for reversal of deep block was 1.77 min (0.83) in patients pretreated with MgSO_4 and 1.98 min (0.58) in those pretreated with placebo ($P = 0.572$). Times to final T1 were longer compared with times to normalized train-of-four ratio 0.9, without any difference between patients pretreated with MgSO_4 or placebo.

Conclusion: Pretreatment with a single intravenous dose of MgSO_4 60 mg/kg does not decrease the efficacy of recommended doses of sugammadex for the reversal of a moderate and deep neuromuscular block induced by an intubation dose of rocuronium. ([ANESTHESIOLOGY 2014; 121:59-67](#))

IN perioperative medicine, intravenous magnesium has been used for the treatment of cardiac arrhythmia,¹ for the control of arterial hypertension during surgery for pheochromocytoma,² as an anticonvulsant for women with preeclampsia and eclampsia,³ for the prevention of postoperative pain,⁴ to accelerate intubation of the trachea,⁵ or as an adjuvant to tracheal intubation without muscle relaxants.⁶ However, intravenous magnesium increases nondepolarizing neuromuscular blockade and attenuates reversal with neostigmine.^{7,8} An excess of magnesium has at least three distinct effects on the neuromuscular junction.⁹ First, it decreases the amount of acetylcholine which is liberated at the motor nerve terminals by inhibition of voltage-dependent P/Q-type calcium channels. Second, it diminishes the depolarizing action of acetylcholine at the end-plate. And third, it depresses the excitability of the muscle fiber membrane. Magnesium *per se*

What We Already Know about This Topic

- Intravenously administered magnesium sulfate is used for a variety of indications in perioperative medicine
- Elevated plasma magnesium ion concentrations enhance the effects of nondepolarizing neuromuscular blockers and attenuate reversal of those effects by neostigmine

What This Article Tells Us That Is New

- A 60 mg/kg intravenous dose of magnesium sulfate administered before induction of anesthesia had no effect on the ability of recommended doses of sugammadex to reverse neuromuscular blockade produced by an intubating dose of rocuronium after spontaneous recovery to moderate and deep levels of blockade

causes significant neuromuscular blockade only at high plasma concentrations (5 to 10 mM).⁹ Yet, in the presence

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of neuromuscular-blocking agents, much lower magnesium concentrations (≥ 1 mM) may inhibit neuromuscular transmission because in this case more acetylcholine is needed to produce a normal degree of depolarization at the end-plate.^{9–11} Prolongation of the duration of the neuromuscular blockade increases the risk of clinically relevant paralysis postoperatively and may thus compromise patient safety.^{8,12–15} To prevent residual neuromuscular block, reliable pharmacological reversal should be achieved before extubation of the trachea. Classically, anesthesiologists have administered cholinesterase inhibitors (for instance, neostigmine) at the end of surgery to antagonize residual effects of neuromuscular-blocking agents. However, it has been shown that in patients who had received intravenous magnesium, the speed of recovery after antagonizing a vecuronium-induced neuromuscular blockade with neostigmine was decreased by approximately 30%.¹⁶ Also, an intravenous bolus of magnesium 50 mg/kg was shown to reestablish a clinically relevant degree of muscle paralysis in patients who had just recovered from a nondepolarizing neuromuscular block.¹⁷ Unlike cholinesterase inhibitors, sugammadex encapsulates steroidal muscle relaxants. It causes a rapid and complete reversal of the neuromuscular blockade by reducing the action of the muscle relaxant at the pre- and postjunctional nicotinic acetylcholine receptors.¹¹ In patients, sugammadex has been shown to effectively reverse moderate and deep rocuronium-induced neuromuscular block.^{18–21} In animal studies, raising magnesium plasma concentrations by 3.50 to 4.0 mM resulted in a depression of twitch height to 65% of baseline values, and subsequently much higher concentrations of sugammadex were required to reverse a rocuronium-induced block.¹¹ Indeed, uncontrolled clinical observations suggest that doses of sugammadex exceeding 14 mg/kg were needed for the reversal of rocuronium-induced deep neuromuscular block in the presence of magnesium.²² The aim of our study was to test whether doses of sugammadex that are recommended for the reversal of rocuronium-induced neuromuscular block were still adequate in patients who had received intravenous magnesium.

Materials and Methods

The study was approved by the Institutional Ethics Committee (Geneva University Hospitals, Geneva, Switzerland; protocol N° NAC 10–093) and the Swiss agency for therapeutic products (SWISSMEDIC). Written informed consent was obtained from all patients. Data reporting follows the CONSORT 2010 recommendations.²³ The protocol was registered before starting patient enrolment at clinicaltrials.gov (identifier, NCT01440933).

Trial Design

This randomized, controlled, double-blinded trial was designed as two separate studies. In the first part, we aimed to test the hypothesis that after pretreatment with

intravenous magnesium, the time to reverse a moderate neuromuscular block (induced by a standard intubation dose of rocuronium) with a recommended dose of sugammadex (2 mg/kg) was prolonged by 50% or greater. In the second part, we aimed to test the hypothesis that after pretreatment with intravenous magnesium, the time to reverse a deep neuromuscular block (induced by a standard intubation dose of rocuronium) with a recommended dose of sugammadex (4 mg/kg) was prolonged by 50% or greater.

Participants

We recruited patients with American Society of Anesthesiologists physical status I or II, aged 18 to 60 yr, and scheduled for elective surgery at Geneva University Hospitals from September 2011 to May 2012. Only men were included because sex was shown to influence the time course of neuromuscular block induced by rocuronium.²⁴ Patients with a history of allergy to propofol, rocuronium, sugammadex, or magnesium, receiving medications known to influence neuromuscular function (for instance, aminoglycosides or phenytoine), receiving magnesium treatment, with a body mass index less than 19 or greater than 28 kg/m², with expected difficult mask ventilation, or with expected difficult intubation were excluded. Patients needing continuous or repeated rocuronium administration for surgical reasons, and patients not needing any neuromuscular blockade, were not considered.

Interventions

All patients were fasted for 6 h before surgery and received midazolam 7.5 mg orally 1 h before induction of anesthesia. Standard noninvasive monitoring was used.

Patients were randomized to receive pretreatment with intravenous magnesium sulfate (MgSO₄) 60 mg/kg or matching placebo (0.9% physiological saline), using a volumetric infusion pump (Infusomat®; Braun Medical SA, Sempach, Switzerland) over 15 min before induction of anesthesia (fig. 1). Anesthesia was induced with sufentanil 0.2 µg/kg and propofol using a target-controlled infusion system (Base Primea; Fresenius-Vial, Brezins, France) using the pharmacokinetic model by Schnider *et al.*^{25,26} The targeted effect-site concentration of propofol for induction was 4 ± 1 µg/ml. When the patient lost consciousness, the lungs were normoventilated through a face mask (end-tidal partial pressure of carbon dioxide, 35 to 45 mmHg) with a 50% oxygen–air mixture. After calibration of the acceleromyograph (see Neuromuscular Monitoring), a single intravenous dose of rocuronium 0.6 mg/kg was administered to all patients, and the trachea was intubated when the first twitch (T1) reached 5% of the baseline value.

No additional rocuronium was administered. Maintenance of anesthesia was with propofol (effect-site concentration, 4 ± 2 µg/ml) and intermittent doses of sufentanil 0.2 µg/kg as required. Body temperature was maintained at 36°C using warming blankets (Bair Hugger®; Arizant Healthcare Inc., Eden Prairie, MN) throughout surgery.

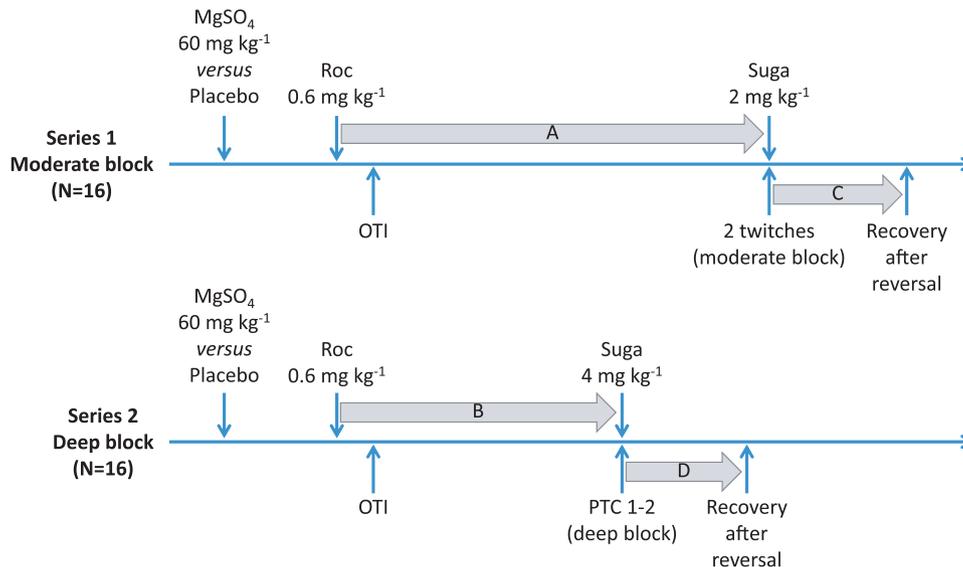


Fig. 1. Study flowchart. The administration of magnesium sulfate (MgSO₄) and placebo was randomized and double blind. The administration of rocuronium (Roc) and sugammadex (Suga) was open. *Gray arrows* represent recorded times. A = Time to spontaneous recovery to two twitches. B = Time to spontaneous recovery to posttetanic count (PTC) 1 to 2. C = Time to total recovery after reversal of moderate block; endpoint was train of four (TOF) ≥ 0.9 , final TOF, and final T1. D = Time to total recovery after reversal of deep block; endpoint was TOF ≥ 0.9 , final TOF, and final T1. OTI = orotracheal intubation.

Neuromuscular Monitoring

Neuromuscular monitoring was carried out according to international guidelines.²⁷ The ulnar nerve was stimulated by train-of-four (TOF) using a TOF-Watch-SX[®] acceleromyograph (Organon Ltd., Dublin, Ireland). Surface electrodes (Red Dot[®] 3M Health Care, Neuss, Germany) were placed on cleaned skin over the ulnar nerve proximal to the wrist. The piezoelectric probe of the acceleromyograph was attached to the tip of the thumb and was secured by placing the thumb in a hand adapter (Hand Adapter[®]; Organon Ltd.).^{28,29} The arm was fixed with an arm-board (arm-board TOF-Guard[®]; Organon Ltd.) and kept in the same position during the study. A temperature sensor, fixed at the distal end of the forearm, ensured that the skin temperature of the monitored arm was maintained at greater than 32°C. Data were registered and stored on a computer using TOF-Watch SX[®] software (version 2.2). After induction of anesthesia, and before administration of rocuronium, TOF stimulation was commenced and repeated every 15 s for 3 min followed by a 5-s tetanic train of 50 Hz. After a pause of 2 min, automatic calibration (CAL-2 mode) was carried out, and TOF stimulation (supramaximal square wave stimuli, 0.2 ms; frequency, 2 Hz) was continued every 15 s.

After stabilization of the neuromuscular measurements (control values), rocuronium 0.6 mg/kg was injected and the trachea was intubated when T1 was 5% of control. No additional rocuronium was given during surgery. In a first series of 16 patients, we allowed spontaneous recovery of two twitches of the TOF before reversal with sugammadex 2 mg/kg. In a second series of 16 patients, early signs of emergence from neuromuscular block were waited for after a posttetanic count stimulation pattern every 5 min (tetanic stimulation during 5 s at 50 Hz followed by 12 single stimuli).

Primary and Secondary Endpoints

Primary endpoint was defined as the time from injection of sugammadex to a normalized TOF ratio of 0.9. Normalization was obtained by dividing TOF ratios at recovery by control TOF ratios measured before the administration of rocuronium.³⁰

Secondary endpoint was the time from injection of sugammadex to final twitch height (T1) (the first of maximal T1 values at stable signal).³¹

Additional Endpoints

Total plasma magnesium concentrations (normal range of concentrations according to the institutional laboratory, 0.65 to 1.05 mM) were determined from freshly drawn venous blood specimens (Synchron[®] Systems Multi Calibrator; Beckman Coulter, Brea, CA) at baseline (*i.e.*, before administration of pretreatments), at the end of administration of pretreatments, and when sugammadex was administered at deep and moderate block.

Postoperatively in the recovery room, oxygen saturation, respiratory rate, heart rate, and noninvasive blood pressure were monitored. We also recorded any clinical sign of muscle weakness.

Sample Size

We assumed that in patients pretreated with placebo, the time required to reverse a moderate rocuronium-induced block with sugammadex 2 mg/kg to TOF ratio 0.9 was on average 2 min (SD, 0.7),^{19,32–34} and that in patients pretreated with magnesium that time would be prolonged by more than 50%, thus to 3 min or more (SD, 0.7). To find a significant difference of at least this amplitude with an α error of 0.05 (β 0.80, one-sided *P* value), seven patients per

group were required. To allow for dropouts, we randomized 16 patients (8 MgSO₄, 8 placebo) in the first series.

We assumed that in patients pretreated with placebo, the time required to reverse a deep rocuronium-induced block to TOF ratio 0.9 with sugammadex 4 mg/kg was on average 3 min (SD, 1.0),^{21,35} and that in patients pretreated with magnesium that time would be prolonged by more than 50%, thus to 4.5 min or more (SD, 1.0). To find a significant difference of at least this amplitude with an α error of 0.05 (β 0.80, one-sided *P* value), six patients per group were required. To allow for dropouts, we randomized a further 16 patients (8 MgSO₄, 8 placebo) in the second series.

Randomization

The randomization sequence was generated by the pharmacy of the Geneva University Hospitals and stratified according to two groups (moderate *vs.* deep block). The randomization sequence was kept by the hospital pharmacy to allow concealment of allocation sequence. One author (C.C.) and two study nurses were responsible for enrollment of patients. Treatments were assigned by one author (C.C.) on the day of surgery.

Blinding

The pharmacy of Geneva University Hospitals provided the study drugs (MgSO₄ *vs.* placebo) in identical and numbered syringes. Patients, care givers who administered the study drugs, and those assessing the endpoints were blinded to the study drugs.

Statistical Methods

Baseline characteristics of the patients are reported according to study drug administered. The efficacy analysis included all subjects who received either placebo, MgSO₄, or any dose of sugammadex and who had at least one efficacy measurement recorded. Efficacy was defined as speed of recovery (in minutes) from the injection of sugammadex to a normalized TOF ratio 0.9.

Data on the primary endpoint (time from injection of sugammadex to a normalized TOF ratio of 0.9 in minutes) were reported as mean (SD) and median (range) and were compared between MgSO₄ and placebo pretreated groups using two-sided Student *t* test for comparison of means or a two-sample Wilcoxon rank sum test for comparisons of medians.

Secondary endpoints and additional analyses were reported similarly. All analyses were performed separately for reversal of moderate and deep block.

All analyses were performed with SATA (Release 10; Stata-Corp LP, College Station, TX), and all tests were two-tailed. Alpha level was set at 5%, and the null hypothesis of equivalence between studied groups was rejected when the *P* value was less than 0.05.

Results

Participant Flow

We enrolled 32 patients; all received the assigned pretreatment. Recovery times after sugammadex administration

could be recorded in all patients. In four patients, data on plasma magnesium concentrations were lacking (two in each pretreatment group).

Baseline Data

Baseline characteristics were similar between groups (table 1). After administration of the pretreatments, but before injection of rocuronium, average TOF ratios were approximately 108% in the first part of the study (reversal of moderate neuromuscular block) and were approximately 116% in the second part of the study (reversal of deep neuromuscular block) (table 1). Average heights of T1 were approximately 99% in the first part of the study and were approximately 92% in the second part (table 1).

Recovery Times after Reversal of Moderate Block

Spontaneous Recovery Times. Spontaneous recovery time from injection of rocuronium to two twitches of the TOF (*i.e.*, the time point of the administration of sugammadex 2 mg/kg) was approximately 50% longer in patients who had received pretreatment with MgSO₄, a difference that was statistically significant (table 2).

Primary Endpoint. There was no difference in average reversal times after the reversal of a moderate block between patients who had been pretreated with MgSO₄ and those who had received placebo (table 2).

Secondary Endpoints. There was no difference in reversal times when an alternative endpoint was chosen (final T1) (table 2).

Recovery Times after Reversal of Deep Block

Spontaneous Recovery Times. The time from injection of rocuronium to appearance of posttetanic count 1 to 2 (*i.e.*, the time point of the administration of sugammadex 4 mg/kg) was approximately 13% longer in patients who had received pretreatment with MgSO₄, a difference that was not statistically significant (table 3).

Primary Endpoint. There was no difference in average reversal times after the reversal of a deep block between patients who had been pretreated with MgSO₄ and those who had received placebo (table 3).

Table 1. Baseline Characteristics

	Moderate Block		Deep Block	
	MgSO ₄	Placebo	MgSO ₄	Placebo
	n = 8	n = 8	n = 8	n = 8
Age, yr	36.5 (13.8)	25.5 (7.0)	36 (11.3)	42.3 (10.4)
Weight, kg	81.1 (9.4)	76.6 (13.3)	73.9 (5.7)	81.4 (11.4)
Height, cm	183.8 (5.4)	180.9 (6.5)	176.1 (7.8)	178.1 (7.3)
BMI, kg/m ²	23.8 (3.3)	25.7 (2.5)	23.8 (1.4)	25.6 (2.5)
TOF ratio, %	108.3 (5.9)	108.4 (9.8)	115.9 (5.7)	116.4 (5.8)
Height of T1, %	98.8 (10.2)	98.5 (9.9)	92.9 (5.4)	90.3 (6.7)

All numbers are means \pm SDs. There were no significant differences between the treatment groups for any characteristic.

BMI = body mass index; MgSO₄ = magnesium sulfate; TOF = train-of-four; T1 = first twitch of train-of-four.

Table 2. Recovery Times after Reversal of Moderate Block*

Period	MgSO ₄		Placebo	P Value
	n = 8		n = 8	
Baseline data				
A	Spontaneous recovery to moderate block (two twitches of TOF) (min)			
	Mean (SD)	45.1 (6.29)	30.1 (4.87)	<0.001
	Median (range)	45.0 (37.0–56.0)	29.3 (25.0–37.0)	0.002
Primary endpoint				
C	Time from reversal to recovery (min)*			
	Normalized TOF 0.9			
	Mean (SD)	1.69 (0.81)	1.76 (1.13)	0.897
	Median (range)	1.55 (0.70–3.13)	1.45 (0.70–3.93)	0.875
Secondary endpoint				
C	Time from reversal to recovery (min)*			
	Final T1			
	Mean (SD)	7.09 (2.24)	6.57 (2.47)	0.667
	Median (range)	6.38 (3.47–9.70)	6.57 (3.47–9.43)	0.495

Periods A and C: see figure 1.

* Reversal of moderate block was with sugammadex 2 mg/kg.

MgSO₄ = magnesium sulfate; TOF = train-of-four; T1 = first twitch of train-of-four.

Table 3. Recovery Times after Reversal of Deep Block*

Period	MgSO ₄		Placebo	P Value
	n = 8		n = 8	
Baseline data				
B	Spontaneous recovery to deep block (PTC 1-2) (min)			
	Mean (SD)	23.4 (5.04)	20.3 (2.87)	0.150
	Median (range)	24.5 (16.0–31.0)	20.0 (16.0–24.0)	0.140
Primary endpoint				
D	Time from reversal to recovery (min)*			
	Normalized TOF 0.9			
	Mean (SD)	1.77 (0.83)	1.98 (0.58)	0.572
	Median (range)	1.47 (0.95–3.15)	2.01 (1.18–2.97)	0.318
Secondary endpoint				
D	Time from reversal to recovery (min)*			
	Final T1			
	Mean (SD)	8.47 (2.07)	7.09 (1.38)	0.137
	Median (range)	8.41 (6.13–11.7)	7.45 (5.20–8.82)	0.172

Periods B and D: see figure 1.

* Reversal of deep block was with sugammadex 4 mg/kg.

MgSO₄ = magnesium sulfate; PTC = posttetanic count; TOF = train-of-four; T1 = first twitch of train-of-four.

Secondary Endpoints. There was no difference in reversal times when an alternative endpoint was chosen (final T1) (table 3).

Additional Analyses

In patients who had received MgSO₄ pretreatment, average total magnesium plasma concentrations at the end of the administration of the pretreatments were 2.1 times higher compared with that in those who had received placebo (table 4). At the time point of the injection of sugammadex for the reversal of deep block (posttetanic count 1 to 2), magnesium plasma concentrations were 1.8 times higher. At

the time point of the reversal of moderate block, they were still 1.7 times higher.

Average times to final T1 were consistently longer compared with times to normalized TOF ratio 0.9, independent of whether patients had received MgSO₄ or placebo, and independent of whether the reversal of a deep or moderate block was monitored (tables 2 and 3).

Harms

There were no minor or major adverse events reported. There were no cases of reoccurrence of neuromuscular blockade

Table 4. Magnesium Plasma Concentrations

Time point	MgSO ₄	Placebo	P Value
Preinfusion (baseline)	n = 14	n = 14	
Mean (SD)	0.90 (0.08)	0.88 (0.07)	0.551
Median (range)	0.91 (0.77–1.09)	0.86 (0.80–1.04)	0.435
Postinfusion	n = 16	n = 16	
Mean (SD)	1.86 (0.21)	0.88 (0.06)	<0.001
Median (range)	1.85 (1.56–2.27)	0.88 (0.77–0.98)	<0.001
At reversal of deep block	n = 6	n = 8	
Mean (SD)	1.57 (0.27)	0.87 (0.09)	<0.001
Median (range)	1.48 (1.32–2.04)	0.89 (0.75–1.05)	0.002
At reversal of moderate block	n = 8	n = 8	
Mean (SD)	1.52 (0.07)	0.89 (0.06)	<0.001
Median (range)	1.50 (1.43–1.65)	0.89 (0.82–0.98)	<0.001

Plasma concentrations are in mM.
MgSO₄ = magnesium sulfate.

(through continuing neuromuscular monitoring after the injection of sugammadex until the end of surgery, or clinically during patients' stay in the recovery room) or residual neuromuscular blockade.

Discussion

Summary of Results

We evaluated the efficacy of sugammadex for the reversal of rocuronium-induced moderate and deep neuromuscular blockade in surgical patients who had received an intravenous magnesium infusion. We had hypothesized that the efficacy of sugammadex in reversing rocuronium-induced neuromuscular block would be weakened when patients were pretreated with magnesium. We were unable to confirm our hypothesis and there may be several reasons to explain this result.

First, the magnesium regimen may have been too low. The effect of MgSO₄ on the reversal of rocuronium-induced neuromuscular blockade with sugammadex has been investigated *in vitro* and in animal studies.¹¹ In the isolated phrenic nerve-hemidiaphragmatic preparation of the mouse, the doses of sugammadex that resulted in a complete reversal of neuromuscular blockade induced by rocuronium had to be increased when the magnesium concentration was raised in the buffer.¹¹ In the guinea pig, sugammadex reversal of a rocuronium dose that corresponded to three times ED₉₀ was followed by the reestablishment of a neuromuscular block which lasted over 30 min when a MgSO₄ infusion was administered subsequently; this effect could be prevented by doubling the dose of sugammadex.¹¹ We were using a magnesium regimen that has been frequently used in clinical practice, for instance, for the treatment of preeclampsia,³ or cardiac arrhythmia,¹ and intraoperatively for the prevention of postoperative pain.^{4,36} This regimen was shown to significantly prolong recovery times in patients who had received an intubation dose of rocuronium.⁷ In addition, a slightly smaller dose, 50 mg/kg, was shown to

reestablish a clinically relevant degree of muscle paralysis in patients who had just recovered from an intubating dose of rocuronium.¹⁷ We did not monitor neuromuscular function in awake patients before the pretreatments were commenced. We were therefore unable to compare magnesium's effect on the evoked muscle responses before and after the MgSO₄ infusion. Nevertheless, there was no reduction in T1 amplitudes immediately after the MgSO₄ infusion compared with placebo. It has been estimated that the duration of effect of intravenous magnesium was between 45 and 60 min and that effective plasma concentrations were between 1.5 and 2.0 mM.^{17,37} Under experimental conditions, magnesium plasma concentration of 1.0 mM depressed neuromuscular transmission in presence of a neuromuscular-blocking agent.⁹ In the current study, average plasma magnesium concentrations at the time point of reversal were approximately 1.6 mM. Also, there was evidence that magnesium had a pharmacological effect; as expected, time to spontaneous recovery of the rocuronium block to two twitches was significantly prolonged. Despite this obvious effect of magnesium at the neuromuscular junction, no impact on the reversal efficacy of sugammadex was apparent. Plasma magnesium concentrations of 1.3 to 2.0 mM, as in our study, do not cause a neuromuscular block *per se*.⁹ Only in cases where the safety margin of the neuromuscular transmission is reduced, or abolished by a neuromuscular-blocking agent, will these magnesium concentrations induce TOF fade and T1 depression.^{9,11} It remains speculative whether the reversal efficacy of sugammadex would have been weakened when a larger dose, or a continuous infusion, of magnesium had been administered.

Second, the sugammadex regimen may have been too high. We were using recommended doses of sugammadex for the reversal of deep and moderate rocuronium-induced blocks.^{18–21} When these doses of sugammadex are administered, the free rocuronium plasma concentration rapidly declines near to zero and passes the range where magnesium could still depress recovery. However, a sugammadex regimen as low as 0.5 mg/kg was shown to reverse rocuronium-induced neuromuscular blockade at the reappearance of the fourth twitch in response to TOF stimulation, although reversal lasted almost 10 min.²⁹ Unless the amount of sugammadex is sufficient for the encapsulation of almost all rocuronium molecules, magnesium may still prolong recovery.^{11,16,17} It may therefore be prudent not to administer inadequately low doses of sugammadex in patients who had received magnesium.

Finally, our neuromuscular monitoring may not have been sensitive enough to identify an impact of magnesium pretreatment on the reversal efficacy of sugammadex. To ensure adequate dosage of sugammadex, and satisfactory reversal of rocuronium blockade in the presence of magnesium, objective monitoring is indispensable. Quantitative monitoring is of particular importance when low doses of sugammadex are administered.³⁸

Magnesium lowers the height of all twitches of the TOF response and therefore has not much effect on the TOF fade ratio. We have therefore analyzed the time course of changes in the height of the first twitch of the TOF complex (T1) in addition to the fade of the TOF ratio. We measured the time intervals required to final T1 recovery after sugammadex. Comparisons of average times needed to final T1 recovery between patients who had received magnesium or placebo did not reveal any difference. If we accept the premise that single twitch height must exceed a value of 90% of control for neuromuscular recovery to be considered acceptable,³¹ the current study shows a slower reversal of the rocuronium block with sugammadex than previously thought, and independent of whether patients had received magnesium treatment. The majority of relevant investigations have ignored the changes of the T1 single twitch and have not normalized the TOF ratio. In current practice of neuromuscular monitoring and research, this should be taken into account.

Limitations of This Study

This study has some weaknesses. First, we have investigated the efficacy of sugammadex after administration of a single dose of magnesium and a single intubation dose of rocuronium. It may be speculated that a continuous intravenous infusion of MgSO₄, as frequently described in acute pain trials,⁴ may have had an impact on the efficacy of sugammadex in reversing the neuromuscular block. Similarly, it remains unknown whether repeated rocuronium administrations, or a continuous rocuronium infusion, perhaps combined with a concomitant magnesium infusion, may have weakened the efficacy of recommended doses of sugammadex in reversing the block. Second, we have tested magnesium during anesthesia with propofol which is considered to have no impact on neuromuscular block and reversal.³⁹ Volatile anesthetics enhance the neuromuscular block and compromise reversal with neostigmine.⁴⁰ Sugammadex also reverses rocuronium-induced blockade when volatile anesthetics are used.^{29,41} Magnesium in combination with volatile anesthetics may further increase the neuromuscular block and may have an impact on reversal with sugammadex. Third, during recovery from general anesthesia, patients who had received a neuromuscular-blocking agent remain vulnerable to a variety of agents other than magnesium that interact with neuromuscular transmission.^{42–44} It may be indicated to test the impact of further substances that reduce acetylcholine release, for instance, aminoglycoside antibiotics, on the efficacy of sugammadex for the reversal of rocuronium-induced neuromuscular block. Finally, we have included only men to provide a more homogenous study sample. It remains speculative whether these data may be extrapolated to women. A recently published case report described the successful reversal of rocuronium-induced neuromuscular block with sugammadex in a woman with severe eclampsia who had received an intravenous bolus of magnesium 4 g followed by an intravenous infusion of 1 g/h. Fifty

minutes after the administration of rocuronium 0.85 mg/kg, while posttetanic count was still 0, she received sugammadex 1 g (corresponding to 14.3 mg/kg). Within 5 min, TOF ratio was greater than 0.95 and she was successfully extubated. There were no clinical signs of recurarization.²²

Conclusions

In conclusion, the efficacy of recommended doses of sugammadex for the reversal of moderate and deep rocuronium-induced block was preserved despite the administration of a single intravenous infusion of magnesium. We may thus conclude that the recommended doses of sugammadex, that is, 2 and 4 mg/kg, allow for encapsulating almost all rocuronium molecules that are present at the neuromuscular junction. This also suggests that sugammadex, within the recommended dose regimens, not only antagonizes the neuromuscular block but also reestablishes neuromuscular reserve of the patient. Further investigations may be warranted to confirm this hypothesis and to test the relation between TOF ratio fade and T1 depression during antagonism of a neuromuscular block with sugammadex in patients who have received MgSO₄ in the perioperative period.

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Competing Interests

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