

The effects of magnesium sulfate on neuromuscular blockade by cisatracurium during induction of anesthesia

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Abstract

Background During the induction of anesthesia, patients are at risk of aspiration while awaiting full muscle relaxation. Magnesium has been shown to have synergistic effects with neuromuscular blocking drugs. We tested if magnesium, as an adjunct, increases the speed of onset of muscle relaxation, thereby decreasing the risk of aspiration.

Methods Eighty-eight American Society of Anesthesiologists (ASA) physical status 1 or 2 patients were randomly assigned to three groups. Group Mg-0 received 100 mL of normal saline, whereas groups Mg-25 and Mg-50 received magnesium sulfate at doses of 25 and 50 mg/kg, respectively. Anesthesia was induced with thiopental 5 mg/kg and cisatracurium 0.15 mg/kg. A peripheral nerve stimulator and single-twitch test was performed on the ulnar nerve until the twitch responses to stimulation had disappeared, and the times were recorded. Then the patients were intubated and anesthesia was maintained with 100 µg/kg/min of propofol. The intensity of blockade was measured at regular time intervals with the post-tetanic count test.

Results The mean times to muscle relaxation in groups Mg-0, Mg-25, and Mg-50 were 226, 209, and 188 s, respectively ($P = 0.047$). The intensity of the block increased with the dose of magnesium, and remained highest in group Mg-50 at all times measured ($P < 0.05$). The speed of onset and the intensity of muscle relaxation increased as higher doses of magnesium were used.

Conclusion The increased speed of onset of muscle relaxation produced by magnesium is not substantial enough to justify its use in combination with cisatracurium in rapid sequence induction.

Keywords Cisatracurium · Magnesium sulfate · Neuromuscular blockade

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Introduction

During the induction of anesthesia, patients may be at risk of aspiration while awaiting full muscle relaxation. Thus, if the time to onset of muscle relaxation could be decreased,

this risk would be reduced. Succinylcholine is commonly used when the rapid establishment of a secure airway is warranted. However, because serious adverse events are associated with the use of this drug, non-depolarizing muscle relaxants (NDMRs) are often used as a substitute. Unfortunately, the time to onset of action of these drugs is slow, usually taking more than 3 min to see the effect. A number of actions can be performed to speed up the effect of NDMRs, such as using the priming technique and administering high doses of the drugs [1, 2]. It should be noted that the quality of relaxation created with the priming method is lower than that produced with succinylcholine. Moreover, the priming method is associated with side effects that include aspiration, dysphagia, and diplopia [1].

Cisatracurium is a benzylisoquinolinium NDMR with an intermediate duration of action. It has advantages over atracurium, such as causing a lower histamine release [3]. Even though the time to onset of action of these two drugs is relatively long, cisatracurium has a greater latency period than atracurium. If we could enhance the action of cisatracurium, patients could be intubated rapidly by using this drug with the priming technique, with a resultant decrease in the risk of aspiration [4, 5].

Magnesium sulfate is commonly used for the prophylaxis and treatment of preeclampsia and arrhythmias, but it can also enhance the effect of NDMRs [6, 7]. Magnesium can help to reduce the median effective dose (ED_{50}) of NDMRs, resulting in a more rapid onset of their effects. However, magnesium prolongs the time to recover from muscle relaxation [6]. In patients who received magnesium, recovery was delayed after reversal with neostigmine. Magnesium has both pre- and post-synaptic effects that lead to the enhancement of the blockade produced by cisatracurium. High concentrations of magnesium may inhibit presynaptic calcium channels [6]; when activated, these channels are stimulants for the release of acetylcholine. In addition, magnesium ions have an inhibitory effect on post-junctional potentials and decrease the irritability of the muscle fiber membrane [8].

Several studies have been conducted to examine the effect of magnesium on the actions of atracurium, pancuronium, and vecuronium, using the priming anesthesia technique, as well as other methods. However, the results were conflicting [9–11]. To the best of our knowledge, no study has been conducted to investigate the effect of magnesium on the relaxation profile of cisatracurium during induction of anesthesia with the priming technique, until now. In this study, we examined whether the use of magnesium speed the muscle relaxation effect of cisatracurium, and hypothesized that pretreating patients with magnesium would shorten the onset of action of cisatracurium, thus allowing quicker placement of the endotracheal tube.

Patients and methods

Study approval and experimental design

The experimental design and complete study protocol was reviewed and approved by the Medical Research Ethics Committee at Tehran University of Medical Sciences. The study was also registered with the national Iranian Registry of Clinical Trials (<http://www.irct.ir>), IRCT201012135378N1, in accordance with WHO requirements and the International Committee of Medical Journal Editors' initiative. The experimental design was a prospective, double-blind and placebo-controlled study. After the subjects were screened, a member of the study team approached the patients and explained the details of the research project and its potential risks. After obtaining informed consent, a block randomization method (block size of 6) was used by the clinical pharmacist and the patients were randomized into three treatment groups:

1. Controls: Mg-0 Group: 100 mL normal saline without magnesium
2. Mg-25 Group: magnesium 25 mg/kg in 100 mL of normal saline solution
3. Mg-50 Group: magnesium 50 mg/kg in 100 mL of normal saline solution

Inclusion and exclusion criteria

A total of 90 patients between the ages of 18 and 60 years, with American Society of Anesthesiologists (ASA) physical status 1 or 2, were enrolled. Patients who were candidates for elective intra-abdominal surgery under general anesthesia were included. Exclusion criteria included patients with liver disease (increased transaminase levels or prothrombin time), patients with chronic or acute kidney disease with a calculated glomerular filtration rate (eGFR) of less than 75 mL/min, and patients with neuromuscular system disease. Additionally, any patients who were being treated with any drug affecting neuromuscular function were excluded. Hypermetabolic or hypometabolic states such as fever, infection, and hyperthyroidism or hypothyroidism were also criteria for exclusion. Patients with an acid–base disorder, congestive heart failure, or conductive heart problems, and those who were being treated for cardiac arrhythmias were excluded as well.

Patient preparation and anesthesia induction and maintenance

After IV catheter placement, the patients were divided randomly into three groups. Over a 10-min period before the induction of anesthesia, 100 mL of normal saline with or without magnesium was administered according to the

group assignment. Magnesium sulfate 50 % (magnesium 2.025 mmol/mL and a similar concentration of sulfate ion) was purchased in solution form (Shahid Qazi, Tabriz, Iran) and prepared by the research pharmacist prior to its administration. Immediately after the infusion of the study drug, patients received intravenous midazolam at 0.03 $\mu\text{g}/\text{kg}$ and fentanyl citrate at 2 $\mu\text{g}/\text{kg}$ as premedication. Anesthesia was induced by the intravenous administration of sodium thiopental 5 mg/kg, followed by cisatracurium 0.15 mg/kg. Tracheal intubation took place exactly 3 min after the administration of cisatracurium in all patients. Anesthesia was maintained with total intravenous anesthesia (TIVA), using propofol infusion at a rate of 100–200 $\mu\text{g}/\text{kg}/\text{min}$. All patients were mechanically ventilated with a mixture of oxygen and air (fraction of inspired oxygen was 50 %) at a tidal volume of 6–8 mL/kg, and the respiratory rates were adjusted in the 9–14 breaths/min range to maintain end-tidal concentration of carbon dioxide between 30 and 40 mmHg.

Monitoring and data collection

Standard monitoring, including electrocardiogram; oxygen saturation by pulse oximetry; noninvasive arterial blood pressure; and end-tidal concentrations of oxygen, carbon dioxide, and sevoflurane were obtained using a Datex ADU 98/S5 monitor (Datex Ohmeda, Helsinki, Finland). All data were downloaded onto laptop computers for subsequent analysis. Noninvasive arterial blood pressure and heart rate were measured before induction as baseline readings, at the time of the study drug infusion, 2 and 5 min after the completion of infusion, and every 5 min thereafter for a 30-min duration. Patients were monitored for the occurrence of cardiac dysrhythmias and other changes in the electrocardiogram. After the study protocol had been completed and all necessary data had been collected, the skin incision was made and the surgery was started.

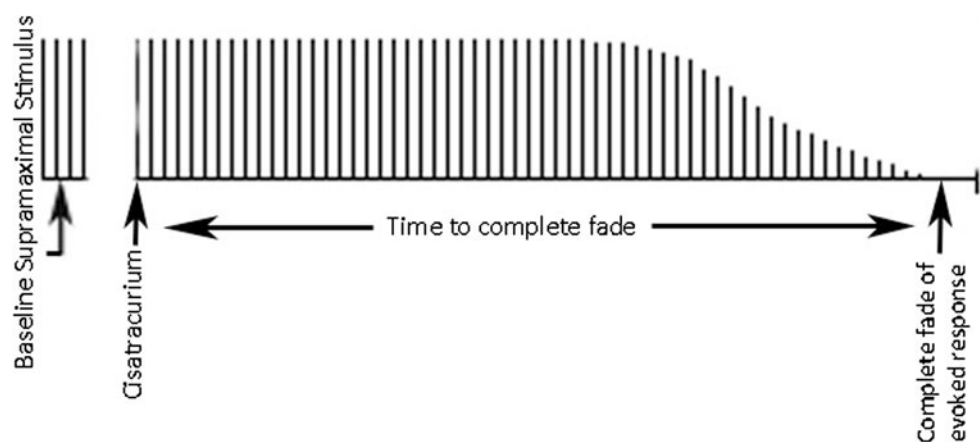
Pattern of nerve stimulation and neuromuscular monitoring

Datex-Ohmeda Model NS252J neuromuscular transmission module (Fisher & Paykel Inc., Auckland, New Zealand) was used to assess neuromuscular function. The monitoring of muscle relaxation was carried out using a peripheral nerve stimulator (Model NS252J; Fisher & Paykel, Auckland, New Zealand). A single square wave supramaximal stimulus, for a period of about 0.2 ms, was delivered to the ulnar nerve at a frequency of 1 Hz and the evoked response of the adductor pollicis muscle was recorded. This muscle was monitored until a complete fade of the twitch response was observed. Two independent anesthesiologists blinded to the treatment recorded this time to complete fade (Fig. 1). Beginning at 2 min after intubation, and then at 5-min intervals until 30 min, the intensity of the neuromuscular block was assessed in all groups, using post-tetanic count (PTC) monitoring; at the same time, vital signs were also recorded. Post-tetanic count monitoring included an initial 5-s tetanic stimulus at 100-Hz frequency, and then a 5-s interval followed by 20 single twitches at a rate of 1 Hz delivered to the ulnar nerve.

Statistical analysis and data management

The sample size was determined by power analysis using the onset of muscle paralysis as the primary outcome variable. The desired effect size was set as a 30 % reduction in time to complete fade; this criterion provided a power of 0.8 with 21 patients in each group. Data were collected into Microsoft Excel 2007 and then were exported into an SPSS 18.0 (SPSS, Chicago, IL, USA) database. Categorical data were analyzed using the χ^2 test and Fisher's exact test; continuous variables were analyzed with two-tailed analysis of variance (ANOVA) and post-hoc intergroup comparison using the Bonferroni test. The null hypotheses were rejected if *P* values were less than 0.05.

Fig. 1 Diagram showing the time to complete fade that was used to measure the onset of neuromuscular blockade produced by cisatracurium



Results

Data from two patients (one from the control group and one from the Mg-50 group) were excluded due to the lack of follow up, and the remaining 88 patients were investigated. There were no differences in the demographic distribution or baseline hemodynamic variables among the three groups (Table 1). The baseline heart rate in all patients was 85 ± 16 bpm, and there were no differences among the treatment and control groups ($P = 0.73$). The baseline mean arterial blood pressure was 101 ± 13 mmHg and was similar in the three groups ($P = 0.34$). Both heart rate and blood pressure remained unchanged after the administration of magnesium, as compared with values in the normal saline controls (Fig. 2).

Overall, dysrhythmias, in the form of premature ventricular contractions, were detected in 6 patients in the Mg-50 group. The incidence of premature ventricular beats was significantly higher in the Mg-50 group when compared with the Mg-0 and Mg-25 groups ($P = 0.005$). However, there was no significant difference between the Mg-0 and Mg-25 groups. Side effects other than dysrhythmias, such

as pain at the injection site, sweating, and flushing were seen in 0, 11, and 16 patients in the Mg-0, Mg-25, and Mg-50 groups, respectively. There was a statistically significant difference in the incidence of the above side effects between the Mg-0 control group and the Mg-25 group ($P = 0.004$), as well as between the Mg-0 control group and the Mg-50 group ($P = 0.001$). However, there was no difference between the Mg-25 and Mg-50 groups ($P = 0.225$). The incidence of movements indicating inadequate relaxation, such as facial grimaces, straining, nasal flaring, and shaking of the body at the time of intubation, was similar in the three groups.

The durations of time to full muscle paralysis (time to complete fade) in the Mg-0, Mg-25, and Mg-50 groups were 226 ± 52 , 209 ± 57 , and 188 ± 58 s, respectively. The onset of muscle relaxant action was significantly shorter in the Mg-50 group when compared with that in the Mg-0 controls ($P = 0.048$); however, there was no statistically significant difference between the Mg-0 and Mg-25 groups (Fig. 3). The numbers of twitches following a tetanic impulse were counted as an indication of the depth of muscle paralysis. All groups demonstrated an early drop in the number of twitches, with the nadir at 10–15 min. The number of twitches increased afterwards, and continued to rise during the 30-min study period (Fig. 4). Repeated measures ANOVA showed a significant difference in PTC among the treatment groups and controls, with a P value of 0.0055. The PTC was lowest in the Mg-50 group at all the time intervals measured.

Table 1 Demographic and hemodynamic data and study groups

| | Mg-0 (N = 29) | Mg-25 (N = 30) | Mg-50 (N = 29) | P value |
|--------------------------|------------------|-------------------|-------------------|---------|
| Age (years) | 39.5 ± 10.6 | 39.8 ± 12.2 | 41.2 ± 12.2 | 0.98 |
| Gender (F/M) | 13/16 | 18/12 | 17/12 | 0.849 |
| ASA PS 1/2 | 20/9 | 16/14 | 17/12 | 0.107 |
| BMI (kg/m ²) | 24.6 ± 3.2 | 24.5 ± 2.9 | 25.0 ± 4.6 | 0.37 |
| Weight (kg) | 73.7 ± 9.7 | 73.3 ± 8.2 | 74.9 ± 13.7 | 0.43 |
| HR (bpm) | 83 ± 17 | 85 ± 14 | 86 ± 17 | 0.73 |
| MAP (mmHg) | 98 ± 11 | 103 ± 15 | 102 ± 13 | 0.34 |

F female, M male, ASA PS American Society of Anesthesiologists physical status, BMI body mass index, HR heart rate, MAP mean arterial pressure

Discussion

The results of the present study showed that the administration of magnesium prior to cisatracurium and the use of the priming method increased the speed of onset of muscle relaxation. This effect of magnesium was dose-dependent,

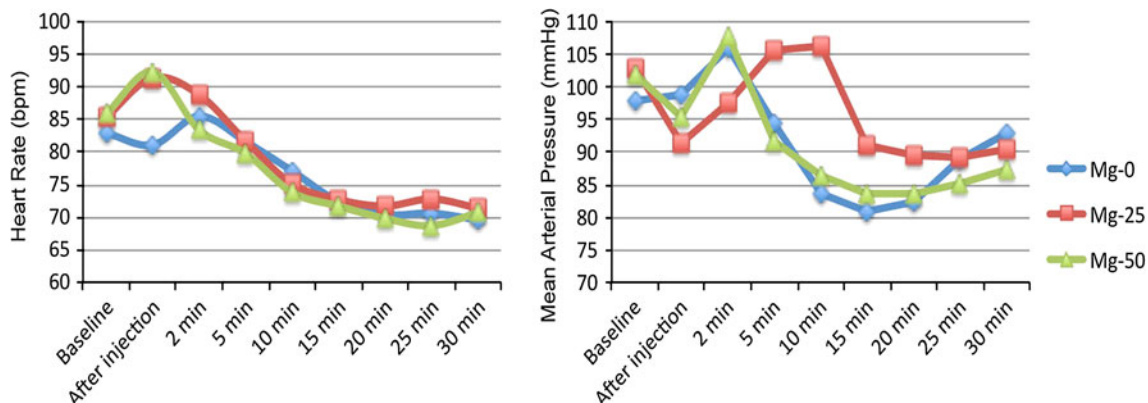


Fig. 2 Hemodynamic changes associated with magnesium injection and administration of cisatracurium

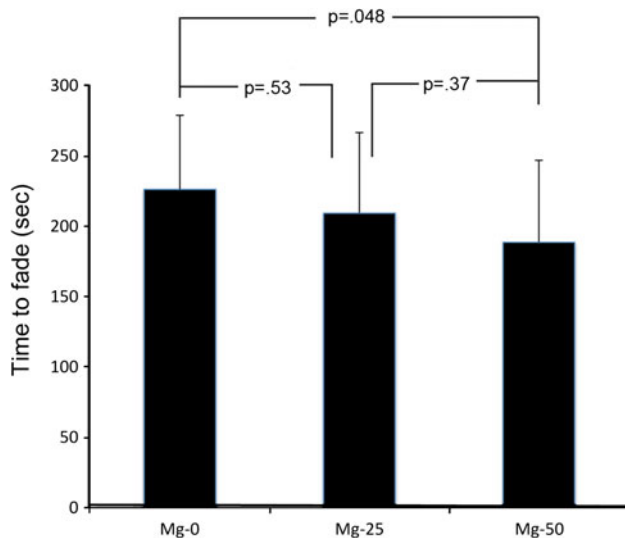


Fig. 3 Time to disappearance of response to single-twitch stimulus. *P* values are shown with each specific comparison

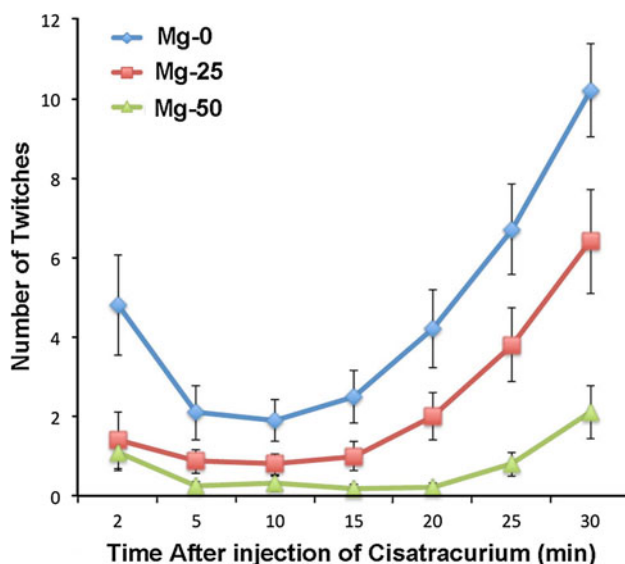


Fig. 4 Post-tetanic count monitoring (PTC), which included an initial 5-s tetanic stimulus at 100-Hz frequency and a 5-s interval followed by 20 single twitches at a rate of 1 Hz delivered to the ulnar nerve. PTC was performed to assess the depth of muscle paralysis. *P* value comparing Mg-0 (saline controls) with Mg-25 (magnesium 25 mg/kg in 100 mL of normal saline solution) was <0.05 from 15 to 30 min after the injection of cisatracurium; *P* value comparing Mg-0 with Mg-50 (magnesium 50 mg/kg in 100 mL of normal saline solution) was <0.01 at all times; and *P* value comparing Mg-25 with Mg-50 was <0.05 from 15 to 30 min after the cisatracurium injection

such that a dose of 50 mg/kg caused a 17 % decrement and a dose of 25 mg/kg resulted in a 7 % decrement in the time to achieve full relaxation. Several studies have investigated the effect of magnesium given before the administration of neuromuscular blocking agents on the speed of onset of muscle relaxation. Our results were similar to those

reported by Wu et al. [12], who showed a faster onset of muscle relaxation by atracurium following a single dose of magnesium at 30 mg/kg. These investigators reported no magnesium-related adverse events. Similarly, other investigators showed decreases in the time to onset of action of neuromuscular blocking drugs, with the exception of rocuronium, following the administration of magnesium, [8, 13, 14].

The potentiating effects of magnesium on muscle paralysis following the use of non-depolarizing neuromuscular blocking drugs continues well into the recovery phase. There are reported cases of recurarization occurring in the recovery room after the parenteral use of magnesium, and these patients required tracheal intubation and mechanical ventilation [15]. Similarly, a recent prospective randomized trial in 21 obese patients showed that a re-established train of four following an intubating dose of rocuronium was suppressed after the administration of magnesium sulfate 50 mg/kg [16].

In a study by Kussman et al. [11] it was concluded that magnesium had no effect on the speed of onset of muscle relaxation produced by rocuronium. This study result was disputed by Czarnetzki et al. [17], who demonstrated that magnesium administered 15 min before anesthesia could reduce the onset time of rocuronium action by 35 %. Czarnetzki et al. [17] attributed the differences between their observations and those in other studies to differences between the studies in the method and timing of magnesium administration; magnesium injected in the form of a bolus immediately prior to the injection of rocuronium did not have time to become evenly distributed at the neuromuscular junction level by the time that rocuronium was administered.

Although we found that magnesium increased the speed of muscle relaxation, the increase was not large enough for us to recommend it as a reliable method for rapid intubation. Although in reality only 90 % suppression of the twitch response is sufficient for intubation, owing to the sensitivity of the methods used in the present study, we measured the time to 100 % loss of the twitch response, and perhaps this was the reason for the observed longer relaxation time.

As expected, magnesium administered prior to cisatracurium increased the intensity of muscle relaxation in a dose-dependent manner. This effect may be important when full relaxation during intubation is required in specific surgeries, such as in the repair of a brain aneurysm. A survey by Pinard and colleagues [9] in 20 patients with elective coronary artery bypass graft (CABG) showed that magnesium prolonged the duration of muscle relaxation with cisatracurium by at least 30–35 min, without changes in hemodynamic stability. Neuromuscular blocking drug-sparing effects of magnesium have been described by Na

et al. [18] in patients with cerebral palsy. Although our results showed an increase in the depth of neuromuscular blockade with the administration of magnesium, the drug-sparing effect of magnesium is beyond the scope of this study.

We observed an increase in the number of dysrhythmias, in the form of premature ventricular beats, in our high-dose magnesium group. Cardiovascular side effects of intravenous magnesium infusion generally include hypotension and flushing. Brady-arrhythmias have occurred at magnesium levels above 10 mEq/L, and these further progress to asystole as levels reach 25 mEq/L. Prolonged PR interval, QRS complex, and QT interval are the most common electrocardiographic changes observed with hypermagnesemia. Although magnesium has been used as an antiarrhythmic medication in clinical medicine, similar ventricular dysrhythmias have been reported by James and colleagues [13] and Pinard et al. [9]. The cardiotoxicity of hypermagnesemia is increased in the presence of hypocalcemia, hyperkalemia, acidosis, digitalis therapy, and renal insufficiency. In the present study, magnesium injection caused mild complications such as pain at the injection site, a feeling of warmth, and sweating. These complications were seen in 55 % of Mg-50 and 37 % of Mg-25 patients, but they were not serious and did not require treatment.

To summarize, although magnesium was able to hasten the muscle-relaxing effect of cisatracurium, in addition to providing a longer duration and increased intensity of the neuromuscular blockade, this increase in speed to muscle relaxation was not significant enough to justify its routine use as a priming agent for cisatracurium in rapid sequence induction. We doubt that there are any potential clinical benefits in adding magnesium to increase the intensity of muscle relaxation, in view of its arrhythmogenic side effects.

References

1. Mehta MP, Choi WW, Gergis SD, Sokoll MD, Adolphson AJ. Facilitation of rapid endotracheal intubations with divided doses of nondepolarizing neuromuscular blocking drugs. *Anesthesiology*. 1985;62(4):392–5.
2. Magorian T, Flannery KB, Miller RD. Comparison of rocuronium, succinylcholine, and vecuronium for rapid-sequence induction of anesthesia in adult patients. *Anesthesiology*. 1993;79(5):913–8.
3. Bryson HM, Faulds D. Cisatracurium besilate. A review of its pharmacology and clinical potential in anaesthetic practice. *Drugs*. 1997;53(5):848–66.
4. Kanaan CA, Estacio RL, Bikhazi GB. Pharmacodynamics and intubating conditions of cisatracurium in children during halothane and opioid anesthesia. *J Clin Anesth*. 2000;12(3):173–6.
5. Deepika K, Kanaan CA, Bikhazi GB, Martineau DB. Influence of the priming technique on pharmacodynamics and intubating conditions of cisatracurium. *J Clin Anesth*. 1999;11(7):572–5.
6. Sinatra RS, Philip BK, Naulty JS, Ostheimer GW. Prolonged neuromuscular blockade with vecuronium in a patient treated with magnesium sulfate. *Anesth Analg*. 1985;64(12):1220–2.
7. Wu QA, Ye YQ. Neuromuscular blockade after therapy with magnesium sulfate and amlodipine. *Eur J Obstet Gynecol Reprod Biol*. 2010;149(2):225.
8. Fuchs-Buder T, Wilder-Smith OH, Borgeat A, Tassonyi E. Interaction of magnesium sulphate with vecuronium-induced neuromuscular block. *Br J Anaesth*. 1995;74(4):405–9.
9. Pinard AM, Donati F, Martineau R, Denault AY, Taillefer J, Carrier M. Magnesium potentiates neuromuscular blockade with cisatracurium during cardiac surgery. *Can J Anaesth*. 2003;50(2):172–8.
10. Nivin FTA. The effect of intraoperative magnesium sulfate infusion on the course of neuromuscular blockade of atracurium. *J Egypt Natl Canc Inst*. 2002;14(2):137–44.
11. 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(1):122–4.
12. Wu HL, Ye TH, Sun L. Effects of atracurium pretreatment with magnesium on speed of onset, duration, and recovery of neuromuscular blockade. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao*. 2009;31(1):73–6.
13. James MF, Schenk PA, van der Veen BW. Priming of pancuronium with magnesium. *Br J Anaesth*. 1991;66(2):247–9.
14. Lampl E, Dandoy M. Priming of atracurium with magnesium. *Br J Anaesth*. 1993;70:A139.
15. Fawcett WJ, Stone JP. Recurarization in the recovery room following the use of magnesium sulphate. *Br J Anaesth*. 2003;91(3):435–8.
16. 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(2):95–9.
17. Czarnetzki C, Lysakowski C, Elia N, Tramer MR. Time course of rocuronium-induced neuromuscular block after pre-treatment with magnesium sulphate: a randomised study. *Acta Anaesthesiol Scand*. 2010;54(3):299–306.
18. Na HS, Lee JH, Hwang JY, Ryu JH, Han SH, Jeon YT, Do SH. Effects of magnesium sulphate on intraoperative neuromuscular blocking agent requirements and postoperative analgesia in children with cerebral palsy. *Br J Anaesth*. 2010;104(3):344–50.