Magnesium sulfate reduces rocuronium dose needed for satisfactory double lumen tube placement condition in patients with myasthenia gravis

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Research article

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Abstract

Background: Using minimum dose of neuromuscular blockade (NMB) to achieve intubation condition is the goal in management of patients with myasthenia gravis (MG). However, tracheal intubation with double lumen tube (DLT) can be challenging if intubation condition is not optimal. This double-blind randomised controlled study was designed to investigate whether magnesium sulfate would reduce rocuronium dose needed and improve the DLT placement conditions for patients with MG who were scheduled for video-assisted thoracoscopic (VATS) thymectomy. Methods: Recruited patients were randomly assigned to receive magnesium sulfate 60mg.kg-1 or normal saline (control) prior to the administration of NMB. Titrating dose of rocuronium was administered to achieve train of four ratio (TOF%) to 10% or below before DLT intubation. The primary outcome was the rocuronium dose required to achieve TOF% below 10%. Secondary outcome was intubation condition for DLT placement. Results: Twenty-three patients had magnesium sulphate and 22 patients had normal saline before rocuronium administration. The required rocuronium dose used were 0.10 (0.05) mg.kg-1 and 0.28(0.17) mg.kg-1 in patients who had magnesium sulphate and normal saline respectively (P<0.0001). With a similar depth of neuromuscular blockade and depth of anaesthesia, 23 patients in the magnesium sulphate group and 16 patients in the control group had excellent intubation condition (P = 0.027). The patients in both groups had similar emergence characteristics. Conclusions: Magnesium sulfate is associated with a decrease in the rocuronium requirement and better DLT intubation condition in patients with MG.

Background

Myasthenia Gravis (MG) is a chronic neuromuscular disease characterized by skeletal muscle weakness. Maximal thymectomy is one of the treatment options recommended for all patients who have mild to moderate muscle weakness due to myasthenia gravis [1]. There are several different approaches for maximal thymectomy, of which right sided video-assisted thoracoscopic (VATS) thymectomy is gaining popularity [2]. Patients with MG are highly sensitive to nondepolarizing neuromuscular blockers [3]. The use of neuromuscular blocker (NMB) in these patients is always difficult and controversial because its use is associated with an increase risk of failed extubation and postoperative respiratory failure [3,4]. However, perioperative stress may also lead to exacerbation of MG and postoperative respiratory failure [4-6].

Rocuronium combined with its specific antagonist, sugammadex, may be a good option for muscle relaxation management for patients with MG, which could largely decrease the risk of failed extubation and postoperative respiratory failure [7-9]. Unfortunately, high price plus other factors such as marketing promotion and local government surveillance limits the clinical use of sugammadex[10], and also some patients may be contraindicated to sugammadex for anaphylaxis reason [11]. Although it is possible to perform an intubation with no NMB, the intubation condition is often unsatisfactory and this may increase the incidence of upper airway injury [12]. In our institution, we routinely titrate small doses of non-depolarizing NMB with train of four ratio (TOF%) of the neuromuscular monitor. Intubation is performed when the TOF% is less than 10%. For patients undergoing VATS, a satisfactory intubation
condition is especially important because the placement of double lumen tube (DLT) demands much better conditions when compared with single lumen tube.

Magnesium sulphate is an agent with analgesic, anaesthetic and NMB effects [13,14]. Previous researches have shown that after the administration of rocuronium, the period of time required to achieve 95% suppression of TOF was shortened if patients were pre-treated with magnesium sulphate [15]. This investigation was designed to evaluate if the use of magnesium sulfate would decrease the dose of rocuronium and improve the intubation conditions in patients with MG. The hypothesis is that the use of magnesium sulphate prior to the administration of rocuronium would reduce the dose required to achieve a satisfactory intubation condition as monitored by TOF%.

**Patients And Methods**

The study was approved by the Hospital Institutional Review Board and registered with the Clinical Trial Registry of China (ChiCTR-1800017696). Patients who were diagnosed with MG of grade I~II of Osserman classification and scheduled to undergo right sided VATS thymectomy were enrolled in this study between May 2016 and May 2018 after written informed consent. The diagnosis was confirmed by the presence of circulating antibody to the acetylcholine receptor, typical clinical and laboratory findings including ptosis, diplopia, limb weakness, and a decremental conduction response on electrical stimulation of the nerve supply to the deltoid muscle. Exclusion criteria included suspected difficult intubation, body mass index >30 kg.m⁻², age less than 18 or over 60 years, hepatic or renal dysfunction, cardiovascular dysfunction, neurologic disorder, operational time over 4 hours, intraoperative blood loss over 1000 ml, history of chronic pulmonary disease, chronic medication with calcium channel blocker or magnesium, and coexisting autoimmune diseases including hyperthyroidism, rheumatoid arthritis, scleroderma or lupus.

The selected patients were randomly assigned to receive magnesium sulfate or normal saline (control). A random sequence was kept within a sealed opaque envelope by a research assistant not involved in this study. On the morning of the surgery, the assistant opened a sealed envelope and prepared the study drug which includes magnesium sulfate (60mg.kg⁻¹ in 50ml normal saline) or 50ml normal saline according to the group allocation. The attending anaesthetists were blinded to their group allocation.

Patients would take their usual dose of anticholinesterase medication and/or steroid on the day of surgery. No premedication was given to the patients. Anaesthesia monitor placed before induction of anaesthesia included pulse oximetry (SpO₂), electrocardiography (ECG), noninvasive blood pressure (NIBP), arterial blood pressure and bispectral index (BIS™ sensor; Medtronic, Minneapolis, MN, USA). Bispectral index was recorded using BISx Power Link™ by Philips Medical Systems (Royal Philips Electronics, Eindhoven, The Netherlands). The arterial blood pressure monitor was achieved with left radial artery cannulation under local anaesthesia. An 18G peripheral venous access was placed after perioperative checklist was performed with the surgical and nursing team. Patients’ vital sign was recorded and could be retrieved from the automatic anesthesia information system.
Anesthesia was induced with $4\mu g.kg^{-1}$ fentanyl and propofol with target controlled infusion (TCI) using Marsh model (Fresenius Kabi AG, Germany). TCI was commenced at effect-site concentration (Ce) of $2\mu g.ml^{-1}$ and titrated to achieve unconsciousness with BIS at 40-60. The patient was ventilated with face masks to maintain the end tidal carbon dioxide between 30-45 mmHg. After the depth of anaesthesia was stable with BIS kept between 40-60 for 10 minutes and a stable Ce of propofol, the electrical stimulation of neuromuscular monitor would be applied at the ulnar nerve for the contraction of the adductor pollicis muscle using train-of-four (TOF) at amplitude 50mA with interval at 20 seconds (ISx Power Link™ by Philips Medical Systems). After the baseline TOF count and TOF% were obtained, the study drug (magnesium sulfate or normal saline) was given over 5 minutes. Another TOF% was obtained after study drug infusion was completed. If the TOF% was above 10%, repeated dose of $0.05mg.kg^{-1}$ rocuronium was given every 3 minutes until the TOF% was lower than 10%. Patient was intubated with DLT using video laryngoscopy when TOF% was less than 10%. The intubation was performed by an experienced anaesthetist. If the tracheal intubation was not successfully accomplished within 20 s, it was recorded as a failed attempt. Mean blood pressure (MAP) and heart rate (HR) were recorded before intubation (Pre-intubation), and after intubation (Post-intubation), the maximum values of MAP and HR within 3 minutes after intubation were also recorded.

Anesthesia was maintained with propofol using TCI to keep BIS at 40-60. Analgesia was achieved with local anesthesia infiltration using 0.5% ropivacaine 10ml before skin incision. Remifentanil TCI infusion at $2\sim4ng.ml^{-1}$ was used intraoperatively. No further dose of NMB was administered after induction. Intravenous 40mg parecoxib was administered at 15-30 minutes before the end of operation for postoperative pain, and 4mg ondansetron plus 5 mg dexamethasone was also used for prevention of postoperative nausea and vomiting (PONV). When the surgery was completed, neostigmine $0.05mg.kg^{-1}$ (along with atropine) and calcium chloride 1g was given to the patient if the TOF% was less than 90% or the anaesthetist was not satisfied with the recovery of the respiratory function. During the operation, $5ml.kg^{-1}.h^{-1}$ Ringer's lactate solution was given and no urine catheter was used. Phenylephrine was used to maintain blood pressure when necessary. All thymectomy were conducted with right sided VATS with three ports. Before closing the final incision for VATS, negative suction of chest cavity combined with lung recruitment maneuvers was employed to re-expand the right collapsed lung, therefore, no postoperative chest drain was used.

The primary outcome of this study was the cumulative rocuronium dose required to achieve TOF% less than 10% before tracheal intubation. The secondary outcome was intubation condition for DLT placement. The DLT intubation condition quality was evaluated based on Copenhagen Consensus Conference scoring system which includes the ease of laryngoscopy, vocal cord position and/or movement and response to intubation or cuff inflation (cough or diaphragmatic movement). Intubation condition was classified as excellent, fair or difficult [16,17]. Other secondary outcomes included were haemodyananic responses to intubation and these included MAP and HR changes (Post-intubation vs. Pre-intubation), propofol concentration during tracheal intubation, time from last dose of rocuronium administration to TOF% returned to 90%, the time to extubation after completion of surgery. Postoperative
data collection included the visual analogue score (VAS) for pain, postoperative Riker sedation and agitation scale and PONV status. We classified the patients’ postoperative pain intensity as no pain, mild pain, moderate pain and severe pain with VAS of 0–4 mm, 5–44 mm, 45–74 mm, and 75–100 mm respectively [18]. Utilizing the Riker sedation and agitation scales, we further divided the patients into three categories according to the scale: over sedated (scales 1 - 2), non-agitated (scales 3 - 4) and agitated (scales 5 - 7) [19,20].

**Statistical analysis**

The sample size estimation was based on the primary outcome (cumulative rocuronium dose used for intubation). In our pilot study before this research was approved by the Hospital Institutional Review Board, the mean difference of the initial rocuronium dose between magnesium sulfate group and normal saline group was 0.14mg.kg\(^{-1}\) with a pooled variance (SD) of 0.11. To obtain an alpha value of 0.05 and a test power of 80%, about 12 subjects were needed in each group. Anticipating about 20% dropout rate, we planned to recruit 30 patients per group.

Continuous variables presented as mean (SD) or number (%) and were compared by Student t-test. Categorical variables are presented as the number of patients and were compared by Chi-square test or Fisher’s exact test. A \(P\) value <0.05 was considered significant. Data analysis was accomplished using MedCalc for Windows, version 11.4.2.0 (MedCalc Software, Mariakerke, Belgium).

**Results**

Sixty-one eligible patients were approached to participate in the study. Nine patients refused to participate, and 3 patients in the magnesium sulphate group and 4 patients in the control group were excluded for incomplete observational data collection or for prolong operation (Fig 1). Finally, 23 patients who received magnesium sulfate and 22 patients who received normal saline were included in the analysis.

Patients’ demographic data including sex, age, BMI, Osserman classification and length of MG history in both groups showed no difference (Table 1). All intubation procedures were achieved with one attempt. No difference was found between the two groups in operation time (Table 1). Pretreatment with magnesium sulphate was associated with a significantly smaller dose of rocuronium required to meet the target depth of neuromuscular blockade (Table 2). What is more, there were 2 patients did not require rocuronium for intubation in the magnesium sulphate group. The intubation condition was significantly better in the patients who had magnesium sulphate (table 2). Moreover, significant fewer patients who had received magnesium sulphate had postoperative agitation (table 2). Tracheal intubation induced a significant increase of MAP and HR in the control group, but not in the magnesium sulphate group (Table 3). There was no difference in other secondary outcomes and those includes the Ce of propofol at intubation, the rate of postoperative neostigmine medication, the time taken for TOF% recovered to 90%,
the time to extubation and postoperative pain intensity (Table 2). There was no reported PONV in post-anaesthesia care unit (PACU).

After the study drug was given, the TOF% of patients in magnesium sulfate group dropped from 95.7% (10.5%) to 77.2% (29.2%), which showed a significant decrease ($p = 0.0095$); whereas the TOF value of patients in the control group was quite stable ($p = 0.211$), changed from 94.7% (12.2%) to 95.9% (9.6%).

The MAP and HR showed no significant change during and after magnesium sulphate infusion.

After the operation, there were 6 patients in the magnesium sulphate group and 7 patients in the control group respectively administered neostigmine for reversal of NMBA. There was no difference in the rate of neostigmine medication. All the patients were extubated in the operation room and transferred to ward after recovery in the PACU. There was no incidence of postoperative myasthenic crisis and re-intubation in any patients.

**Discussion**

Patients with myasthenia gravis are extremely sensitive to nondepolarizing NMBs [3,7]. Very small dose of NMB and residual neuromuscular blockade effect may result in respiratory distress or loss of airway protection during emergence from anesthesia. As a result, some anaesthetists prefer to avoid NMB, whereas intubation without NMBs was reported increasing the risk of difficult tracheal intubation and intubation-related complications [4,5].

The emerge of sugammadex could help to solve the problem between inadequate muscle relax and residual neuromuscular blockade. While sugammadex is not widely used for MG patients for many reasons. In China mainland, less than 10% of the hospital had purchased sugammadex for possible use because it is expensive and not included in the basic medicare drug system. Therefore, using a minimal dose of intermediate-acting NMB is still quite a common choice of tracheal intubation for patients with MG [7,8]. In this investigation, we have revealed that the pre-administration of magnesium sulfate at 60mg.kg$^{-1}$ is associated with a significant decrease in rocuronium requirement with improving tracheal intubation condition for DLT placement.

Magnesium possesses an inhibitory effect on neuromuscular transmission and caused a decrease in muscle fiber membrane excitability. It decreases pre-junctional release of acetylcholine from the motor nerve terminal by decreasing the calcium conductance of presynaptic voltage-dependent calcium channels, and it also reduced sensitivity of the endplate to acetylcholine [21,22]. Magnesium shows significant neuromuscular blockade at high plasma concentrations (5 to 10 mM) or at lower concentrations ($\geq 1$ mM) in the presence of neuromuscular-blocking agents [21,22]. Several studies had showed that magnesium sulphate could decrease the amount of rocuronium required to maintain adequate neuromuscular blockade during different kinds of surgery [23,24]. In our research, magnesium sulfate pretreatment has led to a reduction of TOF% from 96% to 77%, and this has resulted in a significant decrease of the rocuronium dose required to achieve the target TOF%.
Interestingly, patients from the two groups had a similar degree of neuromuscular block, yet the patients in the magnesium sulphate group had better tracheal intubation condition with less hemodynamic change caused by laryngoscopy and tracheal intubation. This may be related to the anti-noxious stimulation effects of magnesium sulfate on the laryngoscopy and tracheal intubation [25]. The mechanism of this action is proved to be inhibition of catecholamine release from adrenal medulla and adrenergic nerve endings [13]. Our results are similar to that of other investigations for single lumen tube placement [26, 27].

Though some research had shown that magnesium sulphate administration is associated with a decrease in the intravenous and inhale anaesthetic dose for induction [13,28], it is not the case in this study. This discordance is possibly related to the small sample size in our study, and magnesium sulphate exerts more enhancement effects on neuromuscular blocker than that of anaesthetic agents.

Though there are two meta-analyses which independently concluded that perioperative systemic magnesium sulphate administration could decrease the postoperative pain scores and opioid consumption [29, 30], we have not observed significant analgesic benefit of magnesium sulphate in this study. This could be related to the lack of continuously infusion of magnesium sulphate during the VATS procedure. Moreover, the overall pain intensity is minimal with the multimodal analgesic regimen, therefore, it would be difficult to detect any difference between the two groups. Significantly more patients in the magnesium sulphate group were comfortable with less agitation and this is consistent with Abdulatif’s finding that magnesium sulphate decreases the incidence and severity of emergence agitation in children undergoing adenotonsillectomy [31].

When selecting a drug for a specific purpose, one should consider the balance between its efficiency and associated side-effects. The most often side effects of magnesium are pain on injection site, hypotension, bradycardia, nausea/vomiting and muscle weakness. Magnesium sulphate (50 - 60 mg.kg\(^{-1}\)) is not associated with serious complications in previous studies [29, 30], and respiratory depression caused by muscle weakness, the most possible dangerous side effect of large dose of magnesium, is not a problem at all in our study. In present research the MAP and HR were stable during and after magnesium sulphate infusion. Combined with the advantage of magnesium sulphate on the decrease of rocuronium dose and improvement of intubation condition for DLT, we suggested that intravenous magnesium sulphate might be an appropriate adjuvant for DLT intubation in patients with MG. Although magnesium sulphate had been extensively investigated as an adjuvant for neuromuscular blocker, this is the first study to describe the benefits of magnesium sulphate on DLT placement in patients with MG.

There are two limitations in this study. The first is that the patients enrolled in our study were classified Osserman I~II and aged less than 60 years. The effects of magnesium sulphate on these patients may be different from that on patients with more severe MG and in patients who are older than 60, therefore our conclusion may not be applied in these patients. The second limitation is related to the titration method of rocuronium, the dose of total rocuronium in the control group was larger than that of the magnesium
sulphate group; thus the duration of rocuronium administration in the control group was longer than that of the magnesium sulphate group. This duration difference resulted in a difference in total anesthesia time and could be a confounding factor for emergence characteristics of the two groups.

In conclusion, the use of magnesium sulfate is associated with a decrease in the rocuronium dose for DLT placement, improvement in the tracheal intubation condition in patients with MG, and improvement in emergence quality with no added adverse event.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Hong Kong University Shenzhen Hospital (approval number [2016]26) on April 8, 2016 and registered with the Clinical Trial Registry of China (ChiCTR-1800017696). We have obtained written informed consents from all of the participants in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The datasets used are also available from Clinical Trial Registry of China (http://www.chictr.org.cn/index.aspx).

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions
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Data analysis: S.J. Fei, X.B.Xu.

Writing paper: S.J. Fei, X.B.Xu.

Revising paper: X.B. Xu.

All authors have read and approved the final manuscript.

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References


15. Kim MH, Oh AY, Jeon YT, Hwang JW, Do SH. A randomised controlled trial comparing rocuronium priming, magnesium pre-treatment and a combination of the two methods. Anaesthesia 2012; 67: 748-54


Tables
Table 1 Patient characteristics. Data are presented as mean (standard deviation) or number of patients.

<table>
<thead>
<tr>
<th></th>
<th>Magnesium sulfate group (n=23)</th>
<th>Normal saline group (n=22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>34.4±11.3</td>
<td>30.3±9.0</td>
<td>0.185</td>
</tr>
<tr>
<td>Body weight</td>
<td>55.8±8.0</td>
<td>60.5±11.0</td>
<td>0.111</td>
</tr>
<tr>
<td>BMI (kg.m-2)</td>
<td>21.7±2.0</td>
<td>22.2±3.0</td>
<td>0.577</td>
</tr>
<tr>
<td>Sex (Male / Female)</td>
<td>4 / 19</td>
<td>7 / 15</td>
<td>0.260</td>
</tr>
<tr>
<td>MG history ≥6 years / &lt;6 years</td>
<td>6 / 17</td>
<td>8 / 14</td>
<td>0.457</td>
</tr>
<tr>
<td>Osserman stage(I / Ila /IIb)</td>
<td>6 / 11 /6</td>
<td>8 / 6 / 8</td>
<td>0.364</td>
</tr>
<tr>
<td>Operation time (minutes)</td>
<td>110.1(31.6)</td>
<td>117.7(24.4)</td>
<td>0.370</td>
</tr>
</tbody>
</table>

* Significant at P=0.05

Table 2 Anesthesia and emergence data. Data are presented as mean (standard deviation) or number of patients.

<table>
<thead>
<tr>
<th></th>
<th>Magnesium sulfate group (n=23)</th>
<th>Normal saline group (n=22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocuronium dosage (mg.kg-1)</td>
<td>0.10 (0.05)</td>
<td>0.28 (0.17)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Intubation condition score (excellent / fair / poor)</td>
<td>23 / 0 / 0</td>
<td>16 / 5 / 1</td>
<td>0.027*</td>
</tr>
<tr>
<td>Propofol concentration when intubation (µg.ml-1)</td>
<td>3.15(0.36)</td>
<td>3.37 (0.91)</td>
<td>0.267</td>
</tr>
<tr>
<td>Time of TOF recovered to 0.9 after the last dose of rocuronium (minutes)</td>
<td>50.5(42.4)</td>
<td>47.2(42.2)</td>
<td>0.881</td>
</tr>
<tr>
<td>Time of extubation time from the end of operation (minutes)</td>
<td>9.4(5.6)</td>
<td>10.5(6.8)</td>
<td>0.561</td>
</tr>
<tr>
<td>Postoperative neostigmine medication (no / yes)</td>
<td>17 / 6</td>
<td>15 / 7</td>
<td>0.672</td>
</tr>
<tr>
<td>Postoperative pain intensity (free / mild / moderate)</td>
<td>15 / 7 /1</td>
<td>8 / 6 / 6</td>
<td>0.056</td>
</tr>
<tr>
<td>Riker sedation and agitation scale in PACU (non-agitated / agitated)</td>
<td>23 / 0</td>
<td>16 / 6</td>
<td>0.009*</td>
</tr>
</tbody>
</table>

* Significant at P=0.05
Table 3 MAP and HR before intubation (Pre-intubation) and after intubation (Post-intubation). Data are presented as mean (standard deviation).

<table>
<thead>
<tr>
<th></th>
<th>MAP (mmHg)</th>
<th>HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Magnesium sulfate group (n=23)</td>
<td>Normal saline group (n=22)</td>
</tr>
<tr>
<td>Pre-intubation</td>
<td>65.6(11.7)</td>
<td>69.5(12.3)</td>
</tr>
<tr>
<td>Post-intubation</td>
<td>69.3(12.3)</td>
<td>86.2(7.42)</td>
</tr>
<tr>
<td>*P</td>
<td>0.309</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

*Significant at *P*=0.05

MAP: Mean arterial blood pressure; HR: heart rate; Pre-intubation: the time point just before starting to intubation; Post-intubation: the time point with the maximum values of MAP and HR within 3 minutes after intubation

**Figures**
Figure 1

Consort flowchart.