Antitussive effect of a magnesium infusion during anesthetic emergence in patients with double-lumen endotracheal tube: a randomized controlled trial

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Background: A double-lumen endotracheal tube (DLT) inserted into the bronchus can stimulate the respiratory tracts, causing coughing. Opioids have been introduced to prevent emergence cough. However, the administration of a significant opioid dose at the end of surgery may result in undesirable events. Magnesium, common intracellular ion, suppress bronchial smooth muscle contraction and have antitussive effect. We investigated the antitussive effects of a magnesium infusion during anesthetic emergence in patients who underwent thoracic surgery requiring one-lung ventilation (OLV) anesthesia with a DLT.

Methods: One-hundred forty patients undergoing OLV anesthesia with a DLT were enrolled in this prospective, randomized double-blinded trial. In combination with a low dose of remifentanil, patients were randomly allocated to receive either magnesium sulphate (infusion of 15 mg/kg/hour after a single bolus of 30 mg/kg) or normal saline during the operation and emergence. Primary outcomes were the severity and incidence of cough during emergence.

Results: The severity of cough was assessed by the cough severity grading score: 0, no cough; 1, single cough; 2, cough persistence <5 seconds; 3, cough persistence ≥5 seconds. There was a significant difference in the severity score of cough between the groups [median (IQR): 2 (0 to 3) in control group *vs.* 0 (0 to 1) in magnesium group, P=0.003]. However, there was no significant difference in the overall incidence of cough between both groups [42 (64.6%) in control group *vs.* 31 (47.7%) in magnesium group, P=0.077].

Conclusions: Magnesium attenuated the severity of cough during emergence after OLV anesthesia using a DLT without adverse events.

Keywords: Complications; cough; magnesium; one lung ventilation; thoracic surgery

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Introduction

Insertion of a double-lumen endotracheal tube (DLT) is considered the standard technique to achieve one-lung ventilation (OLV) (1). However, the DLT has the greater contact area of the respiratory tract, compared with single lumen tube (SLT), can increase the risk for cough reflex during emergence (2-5).

Because coughing during emergence from anesthesia can be associated with adverse events such as laryngospasm, desaturation, and pulmonary edema (6), various methods have been introduced to prevent emergence cough (6-10). Among them, there is sufficient evidence that remifentanil has a beneficial role in suppressing coughing during emergence (6,9,10). Our research team has reported on the effect-site concentrations (Ce) of remifentanil that are ideal for cough suppression during emergence after general anesthesia using DLT: 1.67 ng/mL for 50% of patients and 2.28 ng/mL for 95% (10). However, the administration of a significant opioid dose at the end of surgery may result in adverse events, such as depression of ventilation, delayed awakening, and postoperative nausea and vomiting (6). As such, some limitations must be placed on increases to opioid doses administered during emergence.

Magnesium, the common intracellular ion in human being, has a fundamental role in enzymatic reactions, neurotransmission, and cell signaling (11,12). It also inhibits bronchial smooth muscle contractions (11,13-15) and has been considered an alternative asthma treatment for this reason (11,16). Recently published randomized controlled trials have reported an antitussive effect of magnesium on opioid-induced cough (17,18). However, there have been no studies on the role of magnesium in preventing emergence cough.

Searching for possibilities to prevent emergence cough with minimal adverse effects, we hypothesized that an infusion of magnesium, in combination with a low dose of remifentanil, would be more effective in suppressing emergence cough than remifentanil alone. As such, in this prospective, randomized, double-blinded study, we investigated the antitussive effects of magnesium during recovery from anesthesia in patients who underwent OLV anesthesia with a DLT.

We present the following article in accordance with the CONSORT reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-1977).

Methods

The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. The study was approved by the Institutional Review Board (Ref: AJIRB-MED-OBS-17-184, registration date: July 25, 2017). After written informed consent was obtained from participants, we enrolled 140 patients, aged 19–70 years, of American Society of Anesthesiologists physical status class I–II, who were undergoing surgery requiring OLV. The exclusion criteria were a history of asthma, chronic obstructive disease, signs of upper respiratory infection, a difficult airway, and chronic taking angiotensin-converting enzyme inhibitor. This trial was registered in a public trial registry (Clinical Research Information Service, CRIS) under the identification number KCT0002445 (registration date: September 1, 2017). This study was conducted in a tertiary-care hospital (Ajou University Hospital, South Korea) from September 4, 2017 to November 14, 2019.

Before anesthesia induction, participants were randomly assigned to the control (Group C) or the magnesium group (Group M), using a computerized randomization program. The group assignments were sealed in opaque envelopes, and the only investigator responsible for preparing the study drugs was allowed to open the envelopes to do so. The investigator did not participate in the patients' anesthetic management.

Anesthesia was induced using intravenous propofol 2.0 mg/kg and effect-site targeted controlled infusion (TCI) of 1.5 ng/mL remifentanil. Remifentanil infusion began at the time of anesthetic induction. After the patient did not response to verbal command, rocuronium 1.0 mg/kg was given and manual ventilation with 100% oxygen was done for 90 seconds (s). Tracheal intubation was performed in all patients with a 35-Fr. DLT for women and 37-Fr. DLT for men. The correct positioning of DLT was confirmed with fiberoptic bronchoscopy. If repositioning was necessary, the DLT was guided into position via bronchoscope. Cuff pressure was set to 20 to 25 mmH$_2$O with a hand pressure gauge.

Five minutes after induction of anesthesia, either normal saline or magnesium sulphate was administered according to the group allocation. Patients in Group M received 30 mg/kg intravenous magnesium sulphate for 10 min and then 15 mg/kg/hour continuously during the operation and

anesthetic emergence (12). Patients in Group C received the same volume of normal saline over the same period.

To monitor depth of anesthesia, an ADMS® monitoring device (Unimedics CO, Korea) was attached to the front of the patient's head. This monitor provides a Unicon index of the quantitative electroencephalogram using mono-spectral power analysis, identical to the qCON index, which has been reported to maintain acceptable correlation with the BIS (19,20). Anesthesia was maintained using sevoflurane and TCI of 1.5 ng/mL remifentanil to maintain blood pressure and heart rate within 20% of baseline value, and to maintain a Unicon index of 40 to 60 during surgery. In addition, 0.3 mg/kg/hour rocuronium was continuously administered intravenously to maintain muscular blockade.

Intravenous 400 mg of ibuprofen was administered for pain control, at the beginning of wound closure. After the operation, sevoflurane was discontinued and 4 mg/kg sugammadex was given to reverse neuromuscular (NM) block, while effect-site TCI of 1.5 ng/mL remifentanil was maintained during emergence. When patients were fully awake and opened their eyes in response to a verbal command, the DLT was removed. The patients, who had not regained consciousness by 20 min after sevoflurane had been stopped, were withdrawn from the interventions (remifentanil and study drugs were stopped) and excluded from analysis.

The primary outcomes were the severity and incidence of cough during emergence. Cough, defined as the abdominal muscle contraction, was assessed during anesthetic emergence, which was from immediately after the discontinuation of inhalation anesthetics to 2 min after extubation. The severity of cough was assessed by the cough severity grading score (6): 0, no cough; 1, single cough; 2, cough persistence <5 s; 3, cough persistence ≥5 s. Secondary outcomes were recovery profiles and hemodynamic changes during emergence.

Blood samples were obtained before administration of the study drug and at the end of surgery to measure ionized magnesium level. The times from the discontinuation of inhalation anesthetics to eye opening and to extubation, the end-tidal sevoflurane (ETSevo) concentration at eye opening, and body temperature at the end of surgery were also recorded. Mean arterial pressure, heart rate, and Unicon index were recorded after the completion of the surgery, immediately before and after extubation, and 2 min after extubation. The degree of sedation (0: no response to stimulus, 1: response to loud verbal stimulus or physical contact, 2: responseto general voice, 3: clear consciousness)

and pain score were assessed 30 min after post anesthesia care unit admission. Respiratory complications [bradypnea (<8 breaths/min)] or a hypoxemia (SpO_2 <95% with O_2 supplement) were assessed during the emergence period.

All data were assessed and recorded by an anesthesiologist, who was blind to the group assignments.

Statistical analysis

The sample size calculation was based on a previous study, reporting that the Ce of remifentanil for 50% of patients to prevent cough during emergence after thoracic procedure requiring DLT was 1.67 ng/mL (10). Assuming that an additional infusion of magnesium at about 1.5 ng/mL of remifentanil would reduce the incidence of emergence cough by more than half, 65 patients were required in each group for a type 1 error of 0.05 and a power of 0.8. A total of 140 patients were recruited, based on a predicted drop-out rate of 10%.

All data were expressed as median (IQR), or number of patients (%). The normality of the data distribution was tested using the Kolmogorov-Smirnov test. We conducted Mann Whitney U-tests for continuous variables, and chi-square tests or Fisher's exact test for incidence variables. All statistical analyses were two-sided and performed with R software, version 3.6.1. A significance level of P<0.05 was considered statistically significant.

Results

A total of 140 patients were recruited and assigned to either of two groups. Of these patients, 5 patients in each group were removed from the study. Finally, 130 patients completed all the assessments (*Figure 1*). There was no significant difference in patient characteristics between the groups, excepting height (*Table 1*).

There was a significant difference in the cough severity between the groups. The cough severity grading score is significantly lower in the magnesium group [median (IQR): 2 (0 to 3) in Group C *vs.* 0 (0 to 1) in Group M, P=0.003]. For overall incidence of cough, there was no statistically significant difference between the two groups [42 patients (64.6%) in Group C *vs.* 31 patients (47.7%) in Group M, P=0.077]. However, in the subgroup analysis, the incidence of severe cough (grade 3) was higher in the control group than in the magnesium group [17 patients (26.2%) in Group C *vs.* 5 patients (7.7%) in Group M, P=0.010, *Table 2*].

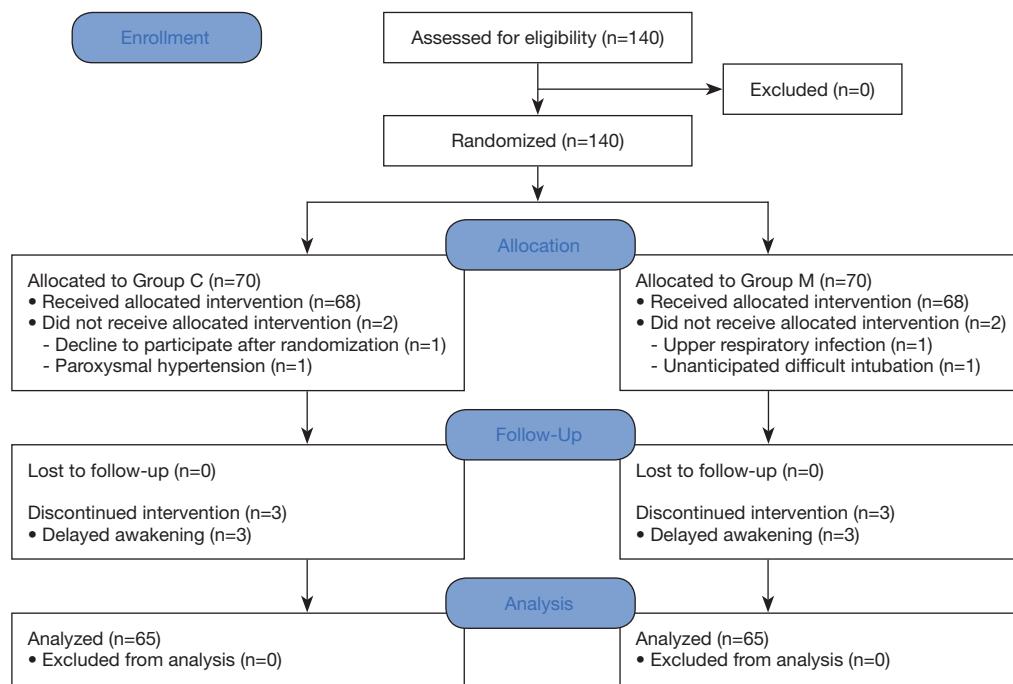There were no differences in recovery profiles, except

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Figure 1 The CONSORT flow diagram.

Table 1 Characteristics and operative data of the patients

Characteristics	Group C (n=65)	Group M (n=65)	P value
Age, years	57.0 (50.0–65.0)	59.0 (52.0–64.0)	0.435
Sex (M/F)	43 (66.2%)/22 (33.8%)	37 (56.9%)/28 (43.1%)	0.367
Weight, kg	65.0 (59.0–71.0)	62.0 (56.0–69.0)	0.120
Height, cm	168.0 (160.0–172.3)	161.0 (157.0–170.0)	0.005
ASA PS, I/II	47 (72.3%)/18 (27.7%)	42 (64.6%)/23 (35.4%)	0.450
Operation			0.807
Lobectomy	40 (61.5%)	45 (69.2%)	
Wedge resection	9 (13.9%)	8 (12.3%)	
Mediastinal mass excision	10 (15.4%)	8 (12.3%)	
Others	6 (9.2%)	4 (6.2%)	
Surgical side (Lt/Rt)	27 (41.5%)/38 (58.5%)	30 (46.2%)/35 (53.8%)	0.724
Intubation attempt (1/2)	64 (98.5%)/1 (1.5%)	60 (92.3%)/5 (7.7%)	0.208
Number of tube reposition (0/1/2)	56 (86.2%)/8 (12.3%)/1 (1.5%)	55 (84.6%)/10 (15.4%)/0 (0%)	0.800
Smoking	20 (30.8%)	13 (20.0%)	0.227
Duration of surgery, min	110.0 (60.0–170.0)	125.0 (95.0–170.0)	0.200
Duration of anesthesia, min	175.0 (110.0–250.0)	195.0 (150.0–241.3)	0.150

Values are presented as median (IQR) or number of patients (%). Group C, control group; Group M, magnesium group; ASA PS, American Society of Anesthesiologists physical status.

Table 2 The severity and incidence of emergence cough

	Group C (n=65)	Group M (n=65)	P value
Cough severity grading score	2 (0 to 3)	0 (0 to 1)	0.003
Overall incidence of cough	42 (64.6%)	31 (47.7%)	0.077
Subjects with severe cough (grade 3)	17 (26.2%)	5 (7.7%)	0.010

Values are presented as median (IQR) or number of patients (%). Cough severity grading score: 0, no cough; 1, single cough; 2, cough persistence <5 s; 3, cough persistence ≥5 s (bucking). Severe cough (grade 3): cough persistence ≥5 s (bucking). Group C, control group; Group M, magnesium group.

Table 3 Comparison of recovery profiles

Factors	Group C (n=65)	Group M (n=65)	P value
Time to eye opening, sec	414.0 (328.5–523.8)	435.0 (285.0–550.0)	0.974
Time to extubation, sec	445.0 (360.0–580.0)	460.0 (320.0–600.0)	0.946
Unicon score			
At the end of surgery	41.0 (34.0–48.0)	43.0 (39.0–48.3)	0.300
Before extubation	82.0 (78.0–90.0)	83.0 (79.0–89.0)	0.350
Immediately after extubation	88.5 (81.3–93.0)	85.0 (81.0–90.5)	0.839
2 min after extubation	89.5 (82.8–95.5)	86.0 (80.5–91.5)	0.245
Temperature at the end of surgery, ℃	35.4 (35.1–35.8)	35.3 (34.8–35.8)	0.151
ETSevo concentration at eye open, vol%	0.3 (0.2–0.4)	0.2 (0.2–0.3)	0.009
Degree of sedation in PACU (1/2/3)	0/10/52	3/13/49	0.258
Pain score	4 (3 to 6)	4 (3 to 6)	0.758

Values are presented as median (IQR) or number of patients. Degree of sedation, 0 = no response to stimulus, 1 = response to loud verbal stimulus or physical contact, 2 = response to general voice, 3 = clear consciousness. Group C, control group; Group M, magnesium group; ETSevo, end-tidal sevoflurane; PACU, post anesthesia care unit.

for ETSevo concentration at eye opening. This was significantly lower in the magnesium group than in control group (*Table 3*).

Concerning hemodynamic parameters, although heart rate was significantly lower in the magnesium group than in the control group during the emergence, no clinically significant hypotension or bradycardia was observed in either group (*Table 4*).

As one would expect, the plasma-ionized magnesium levels measured at the completion of surgery were higher in the magnesium infusion group as compared to the control group [median (IQR): 0.53 (0.47 to 0.57) in Group C *vs.* 0.81 (0.74 to 0.87) in Group M, P<0.001, *Table 5*].

No patients suffered any respiratory complications during the investigation.

Discussion

In this study, we evaluated the antitussive effects of intravenous magnesium during emergence after general anesthesia using DLT. To our knowledge, it is the first study that evaluates the effect of magnesium to prevent emergence cough. Our results showed that magnesium attenuated the severity of cough after OLV anesthesia using DLT. Although the infusion of magnesium didn't reduce the overall cough incidence, it reduced the incidence of severe cough, that is clinically important.

Magnesium has been used as an adjunct to general anesthesia. Various studies have demonstrated that the administration of intravenous magnesium has a beneficial effect of decreasing postoperative pain and reducing analgesic requirements (21-23). Although the mechanism

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Table 4 Comparison of hemodynamic profiles during anesthetic emergence

	Group C (n=65)	Group M (n=65)	P value
MAP, mmHg			
At the end of surgery	81.0 (75.0–91.0)	82.0 (76.0–93.0)	0.631
Before extubation	99.0 (86.0–112.5)	97.0 (87.0–110.0)	0.784
Immediately after extubation	98.0 (89.0–110.0)	98.0 (87.8–107.3)	0.862
2 min after extubation	101.0 (93.0–110.0)	101.0 (88.0–110.0)	0.653
HR, bpm			
At the end of surgery	73.0 (64.0–82.0)	65.0 (58.0–71.0)	<0.001
Before extubation	76.5 (65.0–86.0)	69.0 (58.0–80.0)	0.020
Immediately after extubation	83.0 (75.0–93.0)	77.0 (63.0–86.0)	0.020
2 min after extubation	79.0 (73.0–85.0)	74.0 (64.0–82.0)	0.010

Values are presented as median (IQR). Group C, control group; Group M, magnesium group; MAP, mean arterial pressure; HR, heart rate.

Table 5 Changes in plasma ionized magnesium levels

	Group C (n=65)	Group M (n=65)	P value
Baseline, mmol/L	0.53 (0.49–0.58)	0.56 (0.52–0.60)	0.174
After infusion, mmol/L	0.53 (0.47–0.57)	0.81 (0.74–0.87)	<0.001

Values are presented as median (IQR). The reference range for ionized magnesium is 0.44–0.59 mmol/L. Group C, control group; Group M, magnesium group.

through which systemic magnesium produces anti-nociceptive effects is still unclear, it is presumed that magnesium inhibits calcium influx, by acting as a calcium channel blocker (CCB) (15,24) and that it is an antagonist of N-methyl-d-aspartate glutamate (NMDA) receptors (11,22).

To date, two randomized controlled trials have evaluated the antitussive effect of magnesium (17,18). These studies investigated the inhibitory effects of magnesium on opioid induced cough during anesthetic induction and demonstrated that magnesium could reduce the incidence and severity of cough caused by opioid. In contrast to these studies, intravenous infusion of magnesium in the present study didn't reduce the incidence of cough, but only alleviated the severity of emergence cough after general anesthesia using DLT. We speculate that these findings may be due to differences in the mechanisms of cough and the intensity of airway irritation. This theory is evidenced by previous studies that have reported the incidence of opioid-induced cough to range from 26% to 65% (25) whereas the incidence of emergence cough after a SLT or a DLT

insertion tends to be somewhat higher, ranging from 72.6% to 90% (6,26-28).

There are several plausible hypotheses to explain why magnesium infusion could alleviate the severity of emergence cough. First, this result may be due to the bronchodilating effect of magnesium. It is well known that magnesium-induced bronchodilation occurs through several mechanisms: (I) inhibition of cholinergic NM transmission, (II) attenuation of calcium-induced muscle contractions, (III) anti-inflammatory activity, (IV) potentiation of agonists acting on adenylyl cyclase, prostaglandin-mediated vascular smooth muscle relaxation, and (V) the blockade of NMDA receptors in the larynx, lung, and airways (15,17,18). Second, magnesium reduces muscle fiber excitability and the amplitude of endplate potential, by acting as a CCB at presynaptic nerve endings and decreasing acetylcholine release at the motor endplate (17,18).

We should consider the other potential effects and actions of magnesium when using magnesium in perioperative management. There is substantial evidence that magnesium potentiates the effect of NM blocking agents (17,18,29)

and that it possesses sedative properties (30). These effects may result in delayed recovery from anesthesia (31). In addition, magnesium can cause cardiovascular side effects, including hypotension and bradycardia, and serious cardiac morbidity (32,33). These side effects of magnesium are dose related (33). The magnesium dose administered in the present study—infusion of 15 mg/kg/hour after a single bolus of 30 mg/kg—are commonly used in the magnesium studies and have proven to be clinically safe (12). In our study, the plasma magnesium concentration after magnesium infusion was high enough compared with other studies (22,23,34), given that it was in an ionized form (35). Also, consistent with previous literature, subjects in our study did not show any delay in recovery or adverse hemodynamic effects after magnesium infusion. Although heart rate was significantly lower in the magnesium group during emergence, no clinically significant hypotension or bradycardia was observed.

Our study had a few limitations that need to be addressed. First, because no studies have been conducted on the effect of magnesium in preventing emergence cough, when selecting the magnesium dose in the present study, we used the magnesium regimen that has been used in previous studies for analgesia in surgical patients (12). Further studies need to be done to reveal the exact magnesium dose in preventing the emergence cough. Second, we did not record the ETSevo concentration during the surgery. Because of the sedative effect of magnesium, the intraoperative ETSevo concentration was probably lower in the magnesium infusion group. This may have resulted in differences in ETSevo concentrations between the two groups at emergence in our study. Third, because all patients in our study were receiving remifentanil with magnesium at the time of anesthesia recovery, it is difficult to draw conclusions regarding the inhibitory effects of magnesium on emergence cough when magnesium is administered alone. Thus, we cannot rule out the effects of interactions, such as the additive or synergistic effects of magnesium and remifentanil. Fourth, muscle relaxation was not monitored using a NM monitor during the study, despite magnesium having been shown to potentiate non-depolarising NM blocking agents. Nevertheless, no clinical prolongation of recovery time was observed in the magnesium infusion group. Fifth, a P value of 0.077 in the overall incidence of coughing clearly points to an underpowered study. Posthoc power analysis revealed 0.50. Claiming that there is absolutely no difference between the groups is a type-II error and wrong conclusion.

Conclusions

Intravenous infusion of magnesium did attenuate the severity of emergence cough but did not reduce the incidence of emergence cough after OLV anesthesia using DLT. In addition, the administered doses of intravenous magnesium infusion did not affect the patient's recovery profile or cause any adverse hemodynamic effects during emergence.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at http://dx.doi.org/10.21037/jtd-20-1977

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-1977). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. The study was approved by the Institutional Review Board (Ref: AJIRB-MED-OBS-17-184) and was registered in a public trial registry (Clinical Research Information Service, CRIS) under the identification number KCT0002445. All patients enrolled completed the informed consent form.

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