Oral Magnesium Lozenge Reduces Postoperative Sore Throat

A Randomized, Prospective, Placebo-controlled Study

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ABSTRACT

Background: Postoperative sore throat (POST) is an undesirable complaint after orotracheal intubation. Magnesium is a noncompetitive *N*-methyl-D-aspartate receptor antagonist thought to be involved in the modulation of pain. The present study aimed to investigate the effect of preoperative administration of oral magnesium lozenge on POST.

Methods: Seventy patients undergoing orthopedic surgery were randomly allocated into two groups, to either receive placebo (control) or magnesium lozenges (magnesium) to be dissolved by sucking 30 min preoperatively. Patients were assessed for incidence and severity (four-point scale, 0–3) of POST at 0, 2, 4, and 24 h postoperatively. The primary outcome was sore throat at 4 h after surgery. The secondary outcome was the severity of POST at four evaluation timepoints postoperatively.

Results: The incidence of POST at 4 h was higher in control group than in magnesium group (95% CI: 26%, 14–42%; $P = 0.032$). The highest incidence of POST occurred at the second hour after surgery, with the rate of 23% in the magnesium group and 57% in the control group (95% CI: 34%, 20–51%; $P = 0.007$). The severity of POST was significantly lower in the magnesium group at 0 ($P = 0.007$) and 2 h ($P = 0.002$). The incidences of POST at 0 and 24 h and severity scores at 4 and 24 h were not significantly different between the groups.

Conclusions: The administration of magnesium lozenge 30 min preoperatively is effective to reduce both incidence and severity of POST in the immediate postoperative period.

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What We Already Know about This Topic

- Sore throat is a prevalent adverse outcome from endotracheal intubation

What This Article Tells Us That Is New

- Compared with placebo, the administration of magnesium lozenge 30 min preoperatively is effective to reduce both incidence and severity of postoperative sore throat

POSTOPERATIVE sore throat (POST) is a common complaint in patients receiving general anesthesia following orotracheal intubation, with reported incidences of 21–65%.[1,2] Irritation and inflammation of the airway were considered the causes of POST.[3] Although the current treatments are not exactly effective and the symptoms ameliorate without any treatment, the management for preventing POST is still advised because it promotes the patient's satisfaction and affects the activities after discharge from the hospital.[4] Therefore, different agents[3,5–8] with variable success have been used for decreasing both the incidence and severity of POST.

Magnesium has antinociceptive effects that are primarily based on the inhibition of calcium entry into the cell, and blocks the *N*-methyl-D-aspartate-type (NMDA) glutamate receptors.[9] Therefore, magnesium can prevent central sensitization caused by peripheral nociceptive sitimulation. Although previous studies regarding pain have generally focused on the role of spinally located NMDA receptors, NMDA receptors are also known to exist peripherally,[10] and it is possible that inflammation stimulates peripheral NMDA receptors.

There has been substantial evidence that magnesium therapy given *via* intravenous route, either preoperatively or perioperatively, has the adjuvant effects on decreasing postoperative pain and analgesic requirements.[11–13] However, oral route of magnesium, including lozenge form, had never been investigated for postoperative pain, though its efficacy was shown in acute rescue treatments and in preventing both asthma and migraine in adults.[14,15]

The antiinflammatory and antinociceptive properties of magnesium and available data suggest that magnesium may have a potential role in reducing POST. At the time the current trial was designed, oral magnesium lozenge had not been used for preventing POST.

We hypothesize that preoperative oral magnesium lozenge treatment would be effective in reducing sore throat because of its antiinflammatory and antinociceptive effects. Therefore, to test that hypothesis, this current study was aimed to investigate the efficacy of oral magnesium lozenge given 30 min before surgery on reducing POST during 24 h after surgery, when POST was caused by oral tracheal intubation in patients undergoing orthopedic surgery of lower extremities.

Materials and Methods

After approval for the study had been obtained from the Ethics Committee (Meram Medical Faculty, Selcuk University, Konya, Turkey, on June 4, 2009, EC.SEL.281–3687), written informed consent, which included an explanation of the study design and goals, was acquired from all patients.

This prospective, randomized, double-blind, single-center, placebo-controlled, parallel group, and comparative study comprised 70 patients who were selected based on the American Society of Anesthesiologists Physical Status classification system (I and II), aged 18–50 yr. All patients were scheduled to undergo elective orthopedic surgery of the lower extremities during general anesthesia at the Department of Orthopaedic Surgery and Traumatology of the Meram Medical Faculty at Selcuk University, Konya, Turkey, from June to November 2009. To minimize cultural influences or geographical effects on the findings, the study was conducted in the central region of Turkey, and all participants lived in the same region. This clinical study was designed to identify the superiority of a new intervention.

Patients with a history of preoperative sore throat, upper respiratory tract infection, common cold, smoking habit, hepatic and renal dysfunction, pregnancy, allergy to magnesium, more than one attempt at intubation, Mallampati grade more than 2, recent nonsteroidal antiinflammatory drug usage, and those who were receiving chronic treatment with calcium channel blockers or magnesium were excluded from the study.

In preoperative visit, using a computer-generated random number table and the sealed envelope method, patients were randomly assigned in a 1:1 ratio to receive either magnesium lozenge or a placebo. The magnesium group received Magnesium-Diasporal lozenge™ (Med Ilac, Istanbul, Turkey), 610 mg magnesium citrate salt, containing100 mg magnesium-ion content per dose (highly ionized, approximately 100 + mM ionized magnesium), sucrose, cellulose powder, citric acid, xanthan gum, calcium canoate, sodium cyclamate, aromatics, and colorant E104 (Med Ilac, Istanbul, Turkey). The control group received a placebo lozenge, 610 mg, containing sucrose, cellulose powder, citric acid, sodium cyclamate, calcium canoate, xanthan gum, aromatics, and colorant E104, which was indistinguishable in appearance and taste from the one containing magnesium. The lozenges were administered orally, to be dissolved by sucking 30 min preoperatively. The placebo lozenges were prepared by a pharmacist and administered by the anesthesia staff who was unaware of the study. Neither the investigators nor the patients knew the content of the lozenges, and the code was not broken until the completion of the study.

The amount of administered magnesium in this study is slightly lower than the recommended daily allowance (135–210 mg magnesium) developed by the Institute of National Academy of Science for Magnesium in healthy adults,[16] but was similar to the work by Eby,[14] in which 400 mg of magnesium chloride (100 mg magnesium = 100 + mM magnesium ion) was administered in throat lozenges for the treatment and prevention of asthma in adults. Based on the previous studies of different forms of magnesium citrate, it was assumed that the onset of action of magnesium citrate might be between 30 min and 4–6 h;[17–19] therefore we administered the lozenge to be sucked 30 min preoperatively.

None of the patients received any sedative drugs preoperatively. In the operating room, after establishing IV access, routine monitors were applied (electrocardiogram, noninvasive blood pressure, and pulse oximeter). Anesthesia was induced with fentanyl 2 μg/kg and propofol 2 mg/kg with orotracheal intubation facilitated by atracurium 0.5 mg/kg. Neuromuscular block was monitored using train-of-four (Infinity™; Dräger, Lübeck, Germany) stimulations. Atracurium boluses of 0.15 mg/kg were administered when train-of-four count was 2 or more. Endotracheal tubes with a standard cuff (Endotracheal Tube, Cuffed; Bicakcilar, Istanbul, Turkey) were used. Subsequent laryngoscopies were performed by the same anesthesiologist (HB, who had more than 5 yr of experience in anesthesiology) in both groups, using standard 3 or 4 Macintosh metal blades to visualize the larynx. The view was classified using the Cormack–Lehane classification as follows: grade 1, no difficulty; grade 2, only posterior extremity of the glottis visible; grade 3, only the epiglottis visible; grade 4, no recognizable structures visible[20] without laryngeal manipulation. The endotracheal tubes were lubricated with tap water. Male patients received endotracheal tubes with an inner diameter of 8.5 mm and female patients received endotracheal tubes with an inner diameter of 7.5 mm. None of the patients failed at intubaton at the first attempt. Duration of laryngoscopy (time from opening mouth to placement of the endotracheal tube) and the intubation time (the interval between the insertion of the laryngoscope blade into the mouth to the inflation of the endotracheal tube cuff) was measured with a chronometer by an anesthetic technician.

Anesthesia was maintained with 1.5 to 2% sevoflurane in 60% N_2O and 40% O_2 mixture; intermittent fentanyl and atracurium were given if required. Soon after the intubation, the cuff was inflated until no air leakage could be heard, with a peak airway pressure at 20 cm H_2O. Intracuff pressure was adjusted every 30 min using a handheld pressure gauge (Sheridon; Kendall Healthcare Products, Mansfield, PA) as required between 20–22 cm H_2O to limit nitrous oxide-related pressure increases. No nasogastric tube was inserted

in any patient. Tramadol 100 mg was administered intravenously immediately before discontinuing sevoflurane and nitrous oxide. At the beginning of the skin closure, residual neuromuscular block was antagonized with neostigmine and atropine.

Upon emergence from general anesthesia, oral secretions were aspirated from the pharynx just before the extubation in all patients. After this procedure, the patients were extubated gently and transferred to the postanesthesia care unit. When arriving at postanesthesia care unit (0 h) and thereafter 2, 4, and 24 h after the surgery, patients were assessed regarding the incidence and severity of POST by an anesthesiologist who was blinded to the study groups. The incidence of POST was obtained from the patients by asking the presence or absence of soreness in the throat, and patients who had experienced any degree of pain were considered to have sore throat. The severity of POST was graded on a four-point scale[6,7] (0–3) as follows: 0, no sore throat; 1, mild sore throat (complained of sore throat only upon inquiry); 2, moderate sore throat (complained of sore throat on his/her own); and 3, severe sore throat (change of voice or hoarseness, associated with throat pain). The primary outcome of this clinical study was sore throat at 4 h after surgery. The secondary outcome included the severity of POST at all evaluation time-points after surgery.

Side effects,[21] if any, were also noted; patients were asked about gastric irritation, diarrhea, and nausea at the same times of the POST evaluation. In order to determine the serum magnesium levels, the blood was obtained from the antecubital vein in glass tubes and the serum magnesium concentrations in the serum samples were measured with routine colorimetric methods on a autoanalyser (DXC-800; Beckman Coulter, Brea, CA) 4 h after the surgery.

Statistical Analysis

All analyses were conducted using SPSS software (Statistical Package for the Social Sciences, version 16.0; SPSS Inc., Chicago, IL). In this clinical trial, the nature of the hypothesis was tested with two-tailed ANOVA. Kolmogorov–Smirnov test was used to test distribution of numeric data. Categorical variables were defined as number and percentage, and analyzed by the chi-square test. Continuous variables are expressed as mean ± SD or mean and interquartile range. The groups were compared using the Mann–Whitney U test for multiple comparisons. P values < 0.05 were considered significant.

During the evaluation period of 24 h after surgery, the incidence of POST between the groups was compared using the chi-square test with Yates' correction. We compared the two groups on the primary outcome of POST at 4 h after surgery, and $P < 0.05$ was considered significant. As secondary analysis, we also compared groups on POST at 0, 2, and 24 h after surgery. $P < 0.017$ was considered statistically significant (*i.e.*, $0.05/3 = 0.017$, Bonferroni correction). The analysis of secondary outcomes (the severity of POST at four evaluation time-points) were adjusted using Mann–Whitney U test with Bonferroni correction between groups, and $P < 0.0125$ was considered statistically significant (*i.e.*, $0.05/4 = 0.0125$). In addition, we also compared all pairs of the four evaluation time-points to adjust for multiple comparisons within groups, and $P < 0.0083$ was considered statistically significant (*i.e.*, $0.05/6 = 0.0083$, Bonferroni correction); 95% CIs were also calculated.

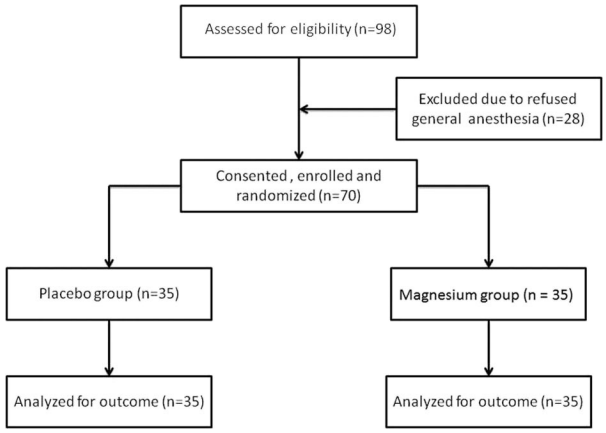

Fig. 1. Flow chart regarding patients involved in the study.

Based on previous studies,[1,2] we presumed the incidence of POST to be 65%. Using power analysis, sample-size calculation revealed that 31 patients per group would be required to detect a 50% reduction in the incidence of POST, with $\alpha = 0.05$ and $\beta = 0.20$ for two-tailed statistical analysis. Therefore, each group included 35 patients.

Results

A total of 98 available patients were screened in the preoperative visit. However, 28 patients refused the study because they wanted to be operated with regional anesthesia. Consequently, 70 eligible patients were randomized (35 received oral magnesium lozenge, and the other 35 patients received placebo) and completed the study. No patient was eliminated from the study because of more than one attempt in intubation, and no patient was lost to follow up the study (fig. 1).

The characteristics of the study groups are shown in table 1; there were no significant differences between the groups with respect to age, weight, gender, and American Society of Anesthesiologists physical status. The intubation time, duration of laryngoscopy, duration of surgery, and duration of anesthesia, fentanyl, and atracurium consumption during the surgery were also similar between the groups ($P > 0.05$). Also, Cormack–Lehane grading scale and postoperative serum magnesium levels did not differ significantly between the groups ($P > 0.05$). As for the potential side effects of magnesium, no gastric irritation, diarrhea, or nausea were observed in any of the patients in magnesium group. No other local or systemic side effects were observed.

Table 2 shows the incidence of POST for the groups at 0, 2, 4, and 24 h after surgery. Within the 24-h period of

Table 1. Patient Characteristics and Intraoperative Variables

Groups	Magnesium (n = 35)	Control (n = 35)
Age (years)	38 ± 7	41 ± 9
Gender (female/male)	24/11	25/10
ASA-PS I/II (*n*)	27/8	27/8
Weight (kg)	58 ± 7	57 ± 8
Duration of anesthesia (min)	84 ± 12	86 ± 9
Duration of surgery (min)	78 ± 11	83 ± 10
Time taken to intubate (min)	2 ± 1	2 ± 1
Duration of laryngoscopy (sec)	10 ± 3	11 ± 3
C-L grading scale (I/II/III/IV)	24/9/2/0	21/13/1/0
Fentanyl (μg), median (range)	100 (50–200)	100 (50–200)
Atracurium (mg/kg/h), intraoperative	0.3 ± 0.06	0.4 ± 0.07
Postoperative serum, Mg (mg/dl)	2.2 ± 0.3	2.1 ± 0.6

Values are shown as number of patients, mean ± SD or median. No significant difference was found between the groups.

ASA-PS = American Society of Anesthesiologists physical status; C-L grading scale = Cormack–Lehane grading scale.

evaluation, the overall incidence of POST was higher in the control group than in magnesium group at 2 and 4 h after surgery ($P = 0.007$ and $P = 0.032$, respectively). When the comparison was made for primary outcome, the magnesium group had significantly lower incidence of POST than control group. The incidence of POST at 4 h after surgery was 40% in control group, but 14% in magnesium group (table 2, 95% CI: 26%, 14–42%; $P = 0.032$). By using Bonferroni correction, the significance criterion was 0.05 for the primary outcome and was 0.017 (0.05/3 = 0.017) for incidence of POST at the other times. The highest incidence of POST occurred 2 h after surgery, with 23% in the magnesium group and 57% in the control group (95% CI: 34%, 20–51%; $P = 0.007$, table 2). There were no significant difference in POST between the magnesium group and the control group at 0 and 24 h after surgery (table 2, 95% CI: 29%, 16–45%; $P = 0.020$, and 95% CI: 20%, 9–36%; $P = 0.047$, respectively). By using Bonferroni correction, the significance level was adjusted to 0.05/3 = 0.017.

The secondary outcomes (the severity of POST) were shown in table 3; by using Bonferroni correction, the significance level was adjusted to 0.05/4 = 0.0125. As compared with the control group, the severity of POST was significantly lower in the magnesium group at 0 and 2 h ($P = 0.007$ and $P = 0.002$, respectively). There were no significant difference in severity of POST at 4 and 24 h ($P = 0.038$ and $P = 0.026$, respectively). When comparing the severity of POST between all pairs of the four evaluation times, no statistically significance was found; a Bonferroni correction was used to adjust for multiple comparisons, and the significance level was adjusted to 0.05/6 = 0.0083.

In the control group, 8 of 35 (23%) patients suffered from severe POST: one patient had hoarseness and one patient had dysphagia at 0 h; one patient had hoarseness and four patients had dysphagia at 2 h; and one patient had dysphagia at 4 h. In addition, throat pain continued in all control group members who suffered from POST. Furthermore, two patients had hoarseness or change of voice, and six patients had dysphagia in the control group. However, no patient suffered from severe POST (change of voice or hoarseness, associated with throat pain) at any evaluation time in magnesium group.

Discussion

The present study showed that oral magnesium lozenge administered 30 min before an operation reduced the incidence of POST, especially at 2 and 4 h after surgery, and also reduced the severity of POST at 2 h postoperatively, after general anesthesia with laryngoscopy and orotracheal intubation. The administration of the oral magnesium lozenge brought about no side effects and did not significantly change serum magnesium levels as compared with the control group.

Postoperative sore throat has a multifactorial etiology, and factors contributing to POST include age, gender, type of surgery, technique of anesthesia, size and cuff pressure of endotracheal tube, pharyngolaryngeal mucosal injury from laryngoscopy, trauma during airway insertion and suctioning, and surgical manipulation of the airway and adjacent

Table 2. Incidence of Postoperative Sore Throat in the Two Study Groups

Evaluation Time	Control Sore Throat (n = 35)	Magnesium Sore Throat (n = 35)	95% CI	*P* Value*
0 h	16 (46%)	6 (17%)	29% (16–45%)	0.020
2 h	20 (57%)	8 (23%)	34% (20–51%)	0.007†
4 h, primary outcome	14 (40%)	5 (14%)	26% (14–42%)	0.032†
24 h	10 (29%)	3 (9%)	20% (9–36%)	0.047

Data are presented as number of patients (n) and percentages (%).

* Using chi-square test with Yates' correction. The significance criterion was 0.05 for the primary outcome (postoperative sore throat at 4 h) and was 0.017 (*i.e.*, 0.05/3, Bonferroni correction) for incidence of postoperative sore throat at the other times. † Statistically significant.

Table 3. Severity of Postoperative Sore Throat in the Two Study Groups

Evaluation Time	Control (n = 35) Severity Score				Magnesium (n = 35) Severity Score				*P* Value*
	0	1	2	3	0	1	2	3	
0 h	19	10	4	2	29	5	1	0	0.007†
2 h	15	12	3	5	27	7	1	0	0.002†
4 h	21	9	4	1	30	5	0	0	0.038
24 h	25	6	4	0	32	3	0	0	0.026

Data are presented as number of patients. Severity score: 0, no sore throat; 1, mild sore throat; 2, moderate sore throat; and 3, severe sore throat. Scores were obtained 0, 2, 4, and 24 h after the surgery. $P < 0.0083$ was considered statistically significant (*i.e.*, 0.05/6).

* Using the Mann–Whitney U test. The significance criterion was 0.0125 (*i.e.*, 0.05/4, Bonferroni correction) for the secondary outcomes (severity of postoperative sore throat at all times). † Statistically significant. A Bonferrroni correction was used to adjust for multiple comparisons within groups. No statistical significance was found in the pairs.

tissue.[5,22] It was demonstrated that pharyngeal, laryngeal, or tracheal irritation leading to inflammation may be the reasons for POST, but POST may occur even in the absence of tracheal intubation.[23] Therefore, it is difficult to determine the exact reason of POST, either by aseptic inflammation or localized trauma that leads to congestion and edema. When taken together, inhaled, topical, or intravenous steroids or other drugs which have antiinflammatory properties have been considered to be beneficial toward treating POST.

In a previous study, Agarwal *et al.*[6] compared the efficacy of dispersible aspirin gargle with benzydamine hydrochloride gargles for prevention of POST. They found that aspirin and benzydamine hydrochloride gargles significantly reduced the incidence and severity of POST. Ozaki *et al.*[5] evaluated the efficacy of transdermal ketoprofen attenuating POST and found ketoprofen applied after anesthesia induction was effective in attenuating the severity of POST. El Hakim[24] compared the effect of beclamethasone inhaler and lidocaine 10% spray on the prevention of POST and found that the incidence of POST was lower than lidocaine spray when administered before tracheal intubation. In another study, Thomas *et al.*[25] showed that 8 mg of intravenous dexamethasone reduced POST significantly as compared with controls. Canbay *et al.*[7] compared the effectiveness of ketamine gargle with placebo in preventing POST after tracheal intubation, and found that ketamine gargle significantly reduced the incidence and severity of POST.

In all of these studies, it was suggested that the reduction in the incidence and severity of POST was related with antiinflammatory effects of the administered drugs. In line with these previous studies, this study found that the magnesium lozenge has reduced incidence and severity of POST. In addition, in our study, the moderate pain was more common and the severe pain was higher in control group at overall evaluation times, except 24 h postoperatively. In the control group, these results can be explained by developing local inflammation, subglottic reactive edema in the membranous vocal cords, and minor granulation tissue. In the magnesium group, the reduction of POST might have resulted from a localized decrease in inflammatory response because of its antiinflammatory effect by decreasing inflammatory markers. Previous studies have suggested that NMDA receptor antagonists have both an analgesic and antiinflammatory role in the management of postoperative pain.[11–13] Magnesium exerts its antiinflammatory effect by decreasing the release of inflammatory mediators such as histamine, thromboxanes, and leukotriens; therefore, it may be useful in controlling inflammation.[10,26–28]

Furthermore, previous studies have focused on the noncompetitive antagonistic action of magnesium on NMDA receptors.[29–33] It has been shown that activation of peripheral NMDA receptors may contribute to masticatory muscle pain and may also play a role in cutaneous and deep tissue pain; therefore, these NMDA receptor antagonists could prove to be effective analgesics for this type of pain.[10,32,34] In the present study, we suggest that the tracheal intubation can activate peripherally acting NMDA glutamate receptors because of elevation of pharyngeal muscle glutamate levels by a mechanical sensitization and trauma.

In previous studies,[11–13] magnesium was usually given as magnesium sulfate infusion, either preoperatively or perioperatively. As compared with previous studies, which assessed the analgesic effects of magnesium in anesthesia, both administration route and compound of magnesium were different in our study. The bioavailability of magnesium, which is an important factor for efficacy of magnesium, depends on the type of magnesium and its administration form. The bioavailability of organic compounds such as magnesium citrate and aspartate is suggested to be significantly better than that of inorganic mixtures, possibly because of greater water solubility. The efficacy is greater when using highly ionized magnesium rather than poorly ionized compounds.[35]

In our study, the pharmaceutical form of magnesium is a lozenge form that contains sodium cyclamate and citric acid as auxiliary substances. During sucking, carbon dioxide production, citric acid, and saliva secretions may provide complete solubility of the magnesium citrate salt so that magnesium becomes readily ionized, which is the active form of magnesium used by tissues. This is essential for local adsorption. In addition, we think that the direct contact of magnesium ions with pharyngeal wall is an important issue. Nevertheless, we suggest that magnesium works locally and it is adhered to the pharyngeal wall. In case of POST, when the process of passing through to the tissue begins, it can also

decrease the edema if it is used as a lozenge form. Thus, its effect might begin immediately when it is contacted with the wall and absorbed from there as long as it stays in the pharyngeal tissue.

There could be another option: that when the lozenge is taken, magnesium released from it results in local concentration of high magnesium ions because magnesium citrate is a highly ionic salt. It would be absorbed into the pharyngolaryngeal area and magnesium ions may be moved positively from the mouth into the pharyngolaryngeal area, like a closed electric circuit, which is also suggested in asthma treatment.[14,36] Magnesium released from the lozenge bypasses the classic circulatory system and has local analgesic and antiinflammatory effects, especially in the presence of alkaline pH, in which magnesium is highly concentrated in inflamed tissue and has minimal systemic absorption. Because of such properties, magnesium lozenge was also used in asthma attacks and treatment by Eby.[14] As mentioned earlier, the important point is the local ionized magnesium concentration, which is suggested to be high when presented in lozenge form for POST.

Several potential limitations of this study should be considered. First, although the sample size seems to be relatively small, we were able to successfully test the primary and secondary outcomes. However, to avoid type I error, it would be better if the sample size was computed from the incidence derived from a meta-analysis of POST. Second, the mechanism of the novel therapy of oral magnesium lozenge is still unknown. Data concerning the pharmacokinetic effects of magnesium citrate lozenge is limited; therefore, it is difficult to point out the exact administration time and dosage. Based on previous data in which different pharmaceutical forms of magnesium citrate were used, the estimated peak effect and duration of action of oral magnesium lozenge was stated. Third, in our study the dosage was empirical, with no pilot data. We used a single dose of magnesium lozenge slightly lower than the recommended daily allowance of magnesium and we also examined its effectiveness on reducing POST.

In conclusion, concerning therapeutic effects, a single dose of oral magnesium lozenge administered 30 min preoperatively can more decrease the incidence and attenuate the severity of POST in the immediate postoperative period. Further studies, especially time and dose-ranging studies with larger study populations, are needed to compare magnesium lozenge with other drugs that have been shown to reduce POST.

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