Efficacy of Adjuvant Magnesium for Posttonsillectomy Morbidity in Children: A Meta-analysis

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Abstract

Objectives. The perioperative administration of magnesium is known to reduce postoperative morbidities in adults, such as pain, agitation, and laryngospasm. The objective is to assess the effects of perioperative magnesium as the adjuvant to tonsillectomy as compared with tonsillectomy in children.


Method. Two authors independently searched databases up to January 2017. We compared perioperative magnesium administration (magnesium groups) with no administration of magnesium (control group). The following outcomes were measured: postoperative pain intensity, analgesics administration, or other morbidities (laryngospasm, agitation, postoperative bleeding) in the postoperative 24 hours. Additionally, to evaluate the discrepancy of effects according to different administration routes, subgroup analyses regarding effects according to systemic or local administration of magnesium were performed.

Results. Nine prospective randomized controlled studies (n = 615) that evaluated the effect of magnesium in children having undergone tonsillectomy met inclusion criteria. Compared with control group, the time for first analgesic requirement was significantly delayed in magnesium groups (standardized mean difference = 0.75; 95% CI, 0.20-1.31; P = .0079). Laryngospasm (log odds ratio = −1.09; 95% CI, −2.11 to −0.07; P = .0036) and agitation score (standardized mean difference = −0.67; 95% CI, −0.97 to −0.36; P < .0001) in the recovery room also significantly decreased in magnesium groups. In subgroup analyses regarding pain and laryngospasm-related measurements, local administration of magnesium was shown to be more effective at reducing postoperative morbidities.

Conclusions. Perioperative magnesium regardless of route may offer pain, agitation, and laryngospasm relief without adverse effects in pediatric tonsillectomy. Based on the high heterogeneity of results within some parameters, further studies need to be performed to affirm these results.

Keywords

magnesium, tonsillectomy, pain, analgesics, nausea, vomiting, laryngospasm, agitation, meta-analysis

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Posttonsillectomy pain is an important problem, as it can cause poor oral intake with subsequent serious complications from dehydration.¹ Emergence agitation is a phenomenon during recovery, and it occurs in up to 80% of children experiencing inhalational anesthetics.² Changed cognitive perception after surgery might be associated with the rapid emergence from sevoflurane and desflurane anesthesia.³ Agitation may be related to various risks, including self-inflicted injury to the pediatric patient or the operation site.⁴ Agitation events delay recovery and discharge and induce unpredictable readmission and increased costs, which are major problems that continue to be under-treated in pediatric patients.⁵

Magnesium functions as an antagonist of N-methyl-d-aspartate glutamate receptors and changes the perception and duration of pain.⁶ During the last few years, the number of studies on the local or systemic use of magnesium has increased following our better understanding of the part of this receptor related to pain pathophysiology.⁷ The results of several recent studies on the use of perioperative magnesium are promising, showing the beneficial efficacy of magnesium on pain and agitation in pediatric patients.⁸ However, other research has shown that magnesium fails to decrease morbidities for children undergoing ear, nose, and throat surgery.²,⁹,¹⁰ Given that tonsillectomy is a

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common operation among pediatric patients, it is necessary to make sure that clinicians conduct efficient methods for decreasing postoperative morbidities. We hypothesized that perioperative magnesium could improve postoperative morbidities such as pain, agitation, and laryngospasm among pediatric patients based on the previous adult trials,10-12 and we aimed to evaluate the evidence for the effect of magnesium on pediatric patients’ experiences (pain intensities, agitation, laryngospasm, and postoperative bleeding) with tonsillectomy in randomized controlled studies.

Materials and Methods

Literature Search Strategy

An electronic database search (PubMed, SCOPUS, Embase, Web of Science, Cochrane) based on the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses) was conducted with the goal of identifying all available studies (up to January 2017) related to perioperative magnesium from inception of administration. The following search terms were used: “tonsillectomy,” “adenotonsillectomy,” “magnesium,” “pain,” “agitation,” “children,” and “analgesics.” Only studies written in English were included. We complemented the keyword-based searches by the combinations of all possible keywords with hand screening of references listed in the retrieved articles. References of searched articles were identified to make sure that no related studies were left out. In the event of missing or incomplete data, attempts were made to request details of the published results directly from the authors. Two reviewers, working independently, scanned all abstracts and titles for candidate studies and removed those not associated with the perioperative magnesium. Institutional review board approval was not required due to the nature of this study.

Selection Criteria

Randomized controlled trials that satisfied the described criteria were eligible for review: the trials had to have studied patients undergoing tonsillectomy procedures and may have involved magnesium administration regardless of route. Studies were not adequate for inclusion if, in addition to adenotonsillectomy, patients underwent other operations, such as nasal and otologic surgery, or if reports were duplicated. Additionally, because visual analog scale (VAS) for pain loses its credibility in children <6 years old,1,13 studies that evaluated degree of pain via a VAS among children <6 years old were excluded. Studies were also excluded from the analysis if clinical outcomes were not clearly described with quantifiable data or if it was impossible to evaluate the adequate data from the described results. According to the PRISMA statement, the 27-item checklist and flow diagram were used to perform transparent and complete reporting of meta-analyses (Figure 1).

Data Extraction and Risk-of-Bias Assessment

Data from studies were abstracted with standardized forms and identified by 2 reviewers working separately. Outcomes for analysis included postoperative pain,1,2,4,10 postoperative (24 hours) pain control medication (doses of postoperative opioids or nonopioid analgesics),5,7,10 time to first pain control medication administration (opioids or nonopioid analgesics),1,7,8 postoperative agitation (agitation scores during recovery),2,4,10 postoperative bleeding (incidence of postoperative bleeding),1,7,9 and laryngospasm (incidence of laryngospasm).1,2,4,7,14 These outcomes in systemic administration of magnesium were compared among perioperative magnesium groups versus a control group (defined as patients receiving conventional pain control agents or sham treatments) during postoperative 24 hours. For analysis of the local administration of magnesium, the outcomes were measured via the comparison of magnesium groups (patients receiving magnesium plus local anesthetics) and control groups (patients receiving local anesthetics alone).

The effect of applied magnesium on postoperative morbidities was assessed per discrete studies of patients following
their departure from the operation room. From the included studies, we abstracted data regarding the number of patients, the grading scale or score used to quantify pain and agitation, the amount of analgesic intake, the time to first analgesics administration, the incidence or percentage of postoperative bleeding and laryngospasm, and the P value of the comparison between the magnesium and control groups. The risk of bias for each study was analyzed with the Cochrane “risk of bias” tool,¹⁵ which assesses the following types of biases: selection (random sequence generation and allocation concealment), performance (blinding of participants and personnel), detection (blinding of outcome assessment), attrition (incomplete outcome data), and reporting (selective reporting).

**Statistical Analysis and Outcome Measurements**

R statistical software (R Foundation for Statistical Computing, Vienna, Austria) was utilized for the meta-analysis of selected studies. For continuous variables, meta-analysis was conducted with the standardized mean difference (SMD). The SMD is used as a summary statistic to standardize the results of the studies to a uniform scale when the studies all assessed the same outcome but measured it in a variety of ways, which suggests that a larger effect size (SMD) indicates that a treatment is more clinically effective. Regarding common cutoff values for SMD, the magnesium effect was considered small when the SMD was < 0.4, moderate when it was lying between 0.4 and 0.7, and large when it was > 0.7.¹⁶,¹⁷ For incidence-related variables, odds ratio was utilized according to the Mantel-Haenszel method.¹⁶ Heterogeneity across enrolled studies was calculated with the $I^2$ test. $I^2 > 50\%$ indicated significant heterogeneity between studies and prevented reliance on a combination of the study results. In these cases, the random effects model was used to generate pooled effects.¹⁸

In addition, subgroup analyses for magnesium effect were performed according to systemic or local administration of magnesium. Those outcomes that did not present a significant level of heterogeneity ($I^2 < 50\%$) were analyzed with the fixed effects model. We used a funnel plot and Egger’s test simultaneously to detect potential publication bias. Additionally, we used Duval and Tweedie’s trim and fill to adjust for missing studies and correct the overall effect size regarding publication bias.¹⁵ Sensitivity analyses were performed to estimate the influence of each study on the overall meta-analysis results.

**Results**

A total of 9 studies with 615 participants were enrolled and evaluated for meta-analysis. The results of bias assessment and study characteristics are described in Table 1. Publication bias was not measured, because the number of trials enrolled was insufficient to properly measure a funnel plot or to perform more advanced regression-based assessments.

Overall patient characteristics could not be calculated exactly, due to incomplete reporting on patient variables among studies. The sample size, mean age, and age range for individual-enrolled studies are presented in Table 1.

**Administration of Magnesium vs Control (Postoperative Pain Outcomes)**

Postoperative pain at 15 minutes (SMD = $-0.26, P = .0476$ [k = 6]) and 24 hours (SMD = $-0.39, P = .0155$ [k = 6]) was statistically decreased in the magnesium group compared with the control group. However, there was no significant difference between groups for postoperative pain at 1 hour (SMD = 0.05, $P = .8994$ [k = 9]). Because there was significant interstudy heterogeneity in pain scores at 1 hour and 24 hours ($I^2 > 50\%$), these outcomes were assessed with a random effect model taking into consideration the variation between and within the studies. By contrast, pain score at 15 minutes showed insignificant heterogeneity ($I^2 = 40.36\%$) and was assessed with a fixed effect model (Figure 2).

Given that administration routes (systemic vs local) would be a confounding factor related to high heterogeneity, subgroup analyses were conducted. The effects of systemic and local administration on postoperative pain showed the reciprocal pattern with the lapse of time (decreasing effect pattern of systemic administration and increasing effect pattern of local administration). Analysis of magnesium effect according to the route of administration in postoperative periods demonstrated that the route potentially influences outcomes (Table 2).

**Administration of Magnesium vs Control (Other Outcome Measures)**

The amounts of analgesic required (SMD = $-0.39, P = .0155$ [k = 5]) during the postoperative period (0-24 hours) were significantly decreased in the magnesium group compared with the control group. The time to first analgesic administration (SMD = 0.75, $P = .0079$ [k = 3]) was significantly longer in the magnesium group than the control group. Because there was significant interstudy heterogeneity in postoperative analgesic requirements and time to first analgesic administration ($I^2 > 50\%$), these outcomes were assessed with a random effect model taking into consideration the variation between and within the studies.

In subgroup analyses according to the routes of magnesium administration, the effects of systemic and local administration presented a different pattern on the amount of analgesic required during a 24-hour postoperative period (ineffective systemic administration and significant and efficient local administration). Analysis of the effect of magnesium related to the route of administration demonstrated that the route potentially influenced analyzed outcomes (Table 3).

Levels of postoperative agitation at 15 minutes (SMD = $-0.31, P = .0285$ [k = 3]) and 60 minutes (SMD = $-0.67, P < .0001$ [k = 2]) were statistically lower in the magnesium group compared with the control group. No significant interstudy heterogeneity was found at any period (within 60
<table>
<thead>
<tr>
<th>Leading Author (Year): Operation Type</th>
<th>Patients per Group, n</th>
<th>Age, y: Sex</th>
<th>Comparison†</th>
<th>Outcome Measure Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Flaherty (2003): Hot tonsillectomy</td>
<td>Magnesium (20) vs</td>
<td>6.2 y (3–12 y): 22 males and 18 females</td>
<td>Systemic magnesium vs control (magnesium, 30 mg/kg, intravenously, 5 min prior to surgery)</td>
<td>Pain scores (OPS score), postoperative analgesic requirement (mg), adverse effect (postoperative bleeding incidence)</td>
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<tr>
<td>including adenoidectomy</td>
<td>control (20)</td>
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<tr>
<td>Vahabi (2012): Cold adenotonsillectomy</td>
<td>Magnesium (55) vs</td>
<td>8.96 y (4–14 y): 60 males and 50 females</td>
<td>Local magnesium vs control (2 mg/kg of magnesium-soaked gauze packing)</td>
<td>Pain scores (CHEOPS score)</td>
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<tr>
<td></td>
<td>control (55)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gulhas (2003): Hot adenotonsillectomy</td>
<td>Magnesium (20) vs</td>
<td>6.7 y (3–12 y): 15 males and 25 females</td>
<td>Systemic magnesium vs control (15 mg/kg of magnesium infusion during 20 min)</td>
<td>Postoperative morbidity (laryngospasm incidence)</td>
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<tr>
<td>including adenoidectomy</td>
<td>control (20)</td>
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<tr>
<td>El-Anwar (2015): Cold tonsillectomy</td>
<td>Magnesium (40) vs</td>
<td>9.1 y (7–13 y): 51 males and 29 females</td>
<td>Local magnesium plus levobupivacaine vs levobupivacaine (2 mg/kg of magnesium infiltrated into the peritonsillar area)</td>
<td>Pain scores (VAS score), postoperative analgesic requirement (mg), time to first analgesia (min), postoperative morbidity (laryngospasm), adverse effect (postoperative bleeding incidence)</td>
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<tr>
<td>including adenoidectomy</td>
<td>control (40)</td>
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<tr>
<td>Mohammed (2011): Cold tonsillectomy</td>
<td>Magnesium (30) vs</td>
<td>9.48 y (8–12 y): 32 males and 28 females</td>
<td>Local magnesium plus levobupivacaine vs levobupivacaine (2 mg/kg of magnesium infiltrated into the peritonsillar area)</td>
<td>Pain scores (VAS score), postoperative analgesic requirement (mg), time to first analgesia (min), postoperative morbidity (laryngospasm)</td>
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<td>including adenoidectomy</td>
<td>control (30)</td>
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<tr>
<td>Apan (2010): Hot tonsillectomy</td>
<td>Magnesium (55) vs</td>
<td>7.35 y (3–16 y): 60 males and 50 females</td>
<td>Systemic magnesium vs control (30 mg/kg of magnesium infusion during operation)</td>
<td>Pain scores (pain/discomfort scale), postoperative morbidity (laryngospasm and agitation)</td>
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<tr>
<td>including adenoidectomy</td>
<td>control (55)</td>
<td></td>
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<tr>
<td>Sun (2015): Cold adenotonsillectomy</td>
<td>Magnesium (20) vs</td>
<td>6.0 y (4–10 y): 29 males and 11 females</td>
<td>Local magnesium plus ropivacaine vs ropivacaine (5 mg/kg of magnesium infiltrated into the peritonsillar area)</td>
<td>Pain scores (CHEOPS score), time to first analgesia (min), postoperative morbidity (laryngospasm), adverse effect (postoperative bleeding incidence)</td>
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<td>control (20)</td>
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<tr>
<td>Abdulatif (2013): Hot adenotonsillectomy</td>
<td>Magnesium (33) vs</td>
<td>5.6 y (4–7 y): 33 males and 32 females</td>
<td>Systemic magnesium vs control (30 mg/kg of magnesium, followed by a continuous infusion of 10 mg/kg/h)</td>
<td>Pain scores (CHEOPS score), postoperative morbidity (laryngospasm and agitation)</td>
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<td>including adenoidectomy</td>
<td>control (32)</td>
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<tr>
<td>Benzon (2015): Hot tonsillectomy</td>
<td>Magnesium (30) vs</td>
<td>6.3 y (4–10 y): 30 males and 30 females</td>
<td>Systemic magnesium vs control (30 mg/kg magnesium, followed by a continuous infusion of 10 mg/kg/h)</td>
<td>Pain scores (PPPM scale), postoperative analgesic requirement (mg), postoperative morbidity (agitation)</td>
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<td>including adenoidectomy</td>
<td>control (30)</td>
<td></td>
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<tr>
<td>Karaaslan (2008): Cold tonsillectomy</td>
<td>Magnesium (25) vs</td>
<td>7.2 y (3–12 y): 25 males and 25 females</td>
<td>Local magnesium plus levobupivacaine vs levobupivacaine (2 mg/kg of magnesium infiltrated into the peritonsillar area)</td>
<td>Pain scores (CHEOPS score), postoperative analgesic requirement (mg), postoperative morbidity (laryngospasm)</td>
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Abbreviations: CHEOPS, Children’s Hospital of Eastern Ontario Pain Scale; OPS, Objective Pain Scale; PPPM, Parents’ Postoperative Pain Measure; VAS, visual analog scale.

†All studies were level of evidence 1 (randomized controlled prospective study). All studies had a low risk of bias.

Mean (approximate range).

*Dosing, duration, and type of magnesium therapy administered.
minutes; \( I^2 < 50\% \) regarding levels of postoperative agitation (Figure 3). There were no significant differences in the incidence of postoperative bleeding (log odds ratio = 0.49, \( P = .6530 \) [k = 3]) within 1-week follow-up periods. However, the incidence of laryngospasm within the recovery room (log odds ratio = \(-1.09, P = .0362 \) [k = 8]) was statistically lower in the magnesium group versus the control group. There was no significant interstudy heterogeneity in these outcomes (\( I^2 < 50\%; \) Table 3). Due to insignificant heterogeneity, the outcomes related to agitation,
postoperative bleeding, and laryngospasm were assessed with a fixed effect model. There were no other adverse effects of magnesium administration reported in the enrolled studies.

**Sensitivity Analyses**

Sensitivity analyses were performed to evaluate whether the pooled estimates of outcomes were different by omitting a different study each time and repeating the meta-analyses. Finally, the results were all consistent with the aforementioned outcomes.

**Discussion**

This study had the main purpose to assess the efficacy of magnesium in reducing posttonsillectomy pain and other morbidity, such as agitation and laryngospasm, in pediatric cases.
patients. In particular, for more reliable results, this study tried to measure the range of pain via behavioral measures of pain as well as the VAS.

Although the VAS is a common pain assessment scale among patients, it is reported that VAS loses its credibility for children < 6 years old.1,13 By contrast, some scoring systems (eg, Objective Pain Scale, Children’s Hospital of Eastern Ontario Pain Scale, Pain/Discomfort Scale, Parents’ Postoperative Pain Measure) are based on the observation by clinicians or parents regarding physiologic, motor, and behavioral responses and are useful for evaluating the degree of pain in patients aged < 6 years old.19,20 In addition, outcomes regarding the administration of posttonsillectomy analgesics were used as objective and alternative criteria for the measurement of pain.21

Our results show that postoperative pain at 15 minutes and 24 hours, as well as the amount of analgesic intake, was statistically diminished in the magnesium group in comparison with the control group and that the time to first analgesic intake was significantly longer in the magnesium group than the control group. Based on time-dependent changes in the effects of magnesium on postoperative pain, the effects of analgesics tended to show a V shape, indicating that any initial analgesic effects gradually decreased and became inefficient after 1 hour but that these effects increased at postoperative 24 hours, eventually regaining efficacy. This tendency seems difficult to explain and is discrepant with the summation of effects of systemic and local administration of magnesium without taking into account the differences in discrete types of magnesium administration.

Interstudy heterogeneity was calculated with the $I^2$ test, and the value of $I^2$ regarding outcomes > 50% indicated significant heterogeneity among studies and prevented reliance on a combination of the study results.18 There was significant interstudy heterogeneity in most measurements regarding pain (postoperative pain at 1 hour, $I^2 = 94.94\%$) and 24 hours ($I^2 = 50.56\%$), first time to uptake analgesics ($I^2 = 68.77\%$), and analgesics amount ($I^2 = 50.56\%$). Because different types of administration would be a confounding factor and show the potential effect on results, subgroup analyses (pertaining to systemic and local administration of magnesium in patients) regarding overall measurements were performed to diminish the heterogeneity and verify factors affecting the results.

The effect of systemic magnesium on postoperative pain disappeared within 1 hour, which is consistent with the explanation of magnesium pharmacokinetics in the work of Vahabi et al.6 That research states that the onset of the effects of magnesium occurs immediately upon the intravenous injection of magnesium and that the duration of effectiveness is 30 minutes. Therefore, during the entirety of 24 hours after an operation, the efficiency of the drug is not thought to last. In contrast, in our study, the local coadministration of magnesium for peripheral blocks mainly enhanced the effects of local anesthetic agents at 24 hours and showed larger effects than the systemic administration of magnesium.15-8 These results are due to 3 reasons. First,
magnesium has peripheral and central effects. During peri-
tonosillar infiltration, magnesium demonstrates local anal-
gesic effects by the blockade of calcium channels in
peripheral nerves (tonsillar nerves), as well as antihyperal-
gesic effects.22 Second, the local anesthetic effects of mag-
nesium are efficacious for >30 minutes, lasting for 24
hours after infiltration, as compared with the systemic phar-
macokinetic effects of magnesium.6-8,22 Third, magnesium
may influence peripheral nerves by interrupting the secre-
tion of neurotransmitter substances at synaptic junctions or
may increase the effect of local anesthetics.22 This tendency
could also explain the subgroup analysis regarding the
analgesic uptake, for which the effects of local magnesium
were highly efficacious in comparison with the systemic
administration of magnesium.

Agitation behavior is potentially injurious for the patient
or the surgical site, with the pulling out of intravenous lines,
drapes, or drains, as well as delays in recovery and
increased duration or personnel required for recovery.2
Although the protective mechanism of magnesium against
agitation is not known accurately, the anticonvulsant effects
of magnesium sulfate can inhibit emergence agitation after
surgery with volatile anesthesia.4 In the findings of this
study, systemic administration of magnesium was effective
in reducing the degree of agitation during time in the recov-
ery room, which is consistent with previous findings about
magnesium pharmacokinetics. Additionally, laryngospasm
is caused by stimulation of the internal muscles of the
larynx. It is reported that the incidence of laryngospasm in
recovery periods is approximately 20% for pediatric aden-
tonosillactomy.1 Magnesium inhibits smooth and skeletal
muscle contraction by way of lessening the amounts of acetyl-
choline secreted from nerve endings.2 In our study, the
summation effects of local and systemic administration of
magnesium show large effect sizes. In particular, local
administration has a significant and large effect size (−1.25,
P = .0246) in comparison with systemic administration (−0.45,
P = .6613). These results are consistent with the action patterns
of magnesium on postoperative pain. This may be explained by
the smooth muscle relaxation that is achieved by local application
of magnesium.

However, many studies have investigated the contradic-
tory effects of magnesium on coagulation factors. Some
authors found that intraoperative magnesium infusion
reduces postoperative hypercoagulability.23 Others found
that intravenous magnesium has no effect on coagulation
factors or fibrinolytic activity.24 Additionally, due to a cal-
cium antagonist, magnesium has a muscle relaxant effect,
which suggests a higher risk of bleeding in some circum-
stances.6 In this study, all types of magnesium administra-
tion (regardless of systemic or local) did not affect
postoperative bleeding, which may suggest that magnesium
administration is safely applicable to pediatric tonsillectomy
without the risk of bleeding among potential postoperative
morbidities.

Although the results of this study offer evidence for the
use of perioperative magnesium in ameliorating patient
morbidities, our investigation should be interpreted within the
context of its limitations. First, to increase the number of
available comparisons, we included studies that evaluate the
effects of magnesium in pediatric patients who underwent
different administration protocols. This fact may have con-
tributed to some of the heterogeneity observed in this study.
We attempted to minimize clinical heterogeneity by including
only randomized controlled studies regarding pediatric aden-
tonosilactomy, and we are able to explain part of the observed
heterogeneity by varying ways of magnesium administration.
Second, the methods of tonsillectomy, such as cold and ther-
mal, are one of the contributing factors in postoperative pain,
which could influence the effect on it differently. However,
the studies that performed thermal tonsillectomy evaluated
the effect of systemic administration of magnesium, and the
studies that performed cold tonsillectomy assessed the local
administration. Third, the enrolled studies regarding topical
effect applied the use of topical anesthetic as perioperative
preparation in the magnesium and control groups. These
limitations could not make the additional subgroup analy-
sis performed. However, the effect size in each study was
calculated as the SMD (intervention vs control) of partici-
pants who underwent the adenotonsillectomy under the
controlled condition to evaluate the effect of magnesium
itself on postoperative pain and other morbidities accord-
ting to the existence or absence of magnesium. The mea-
surement could minimize the influence of other factors of
tonsillectomy and mainly assess the effect of intervention.
Nevertheless, it is necessary to conduct larger trials with a
standardized protocol to draw firmer conclusions.

Conclusion
This meta-analysis demonstrates that local or systemic
administration of magnesium before tonsillectomy in chil-
ren can efficiently decrease posttonsillectomy pain as well
as other morbidities, such as agitation and laryngospasm. It
also shows that magnesium treatment can be utilized with-
out certain adverse effects, such as postoperative bleeding.
In particular, local administration of magnesium is more
effective in reducing postoperative pain and laryngospasm.

Author Contributions
Hye Kyung Cho, study conception and design, acquisition of data,
analysis and interpretation of data, drafting the article and revi-
sions, final approval of article; In Joon Park, study conception
and design, analysis and interpretation of data, drafting the article
and revisions, final approval of article; Ho Young Yoon,
acquisition of data, analysis and interpretation of data, drafting the article
and revisions, final approval of article; Se Hwan Hwang, study
conception and design, acquisition of data, analysis and interpreta-
tion of data, drafting the article and revisions, final approval of article.

Disclosures
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