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Role of topical magnesium in post-operative sore throat: A systematic review and meta-analysis of randomised controlled trials

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Review Article

Role of topical magnesium in post-operative sore throat: A systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Background and Aims: Post-operative sore throat (POST) is a common undesirable consequence of tracheal intubation. Magnesium, an N-methyl-D-aspartate receptor antagonist, has anti-nociceptive and anti-inflammatory properties, and has been found to be useful in POST prevention in various trials. We conducted this systematic review and meta-analysis to study the efficacy of topical magnesium in preventing POST in adult patients undergoing surgery under general anaesthesia with single lumen tracheal tube. **Methods:** Comprehensive literature search was performed in PubMed, Google Scholar, EMBASE, Scopus and the Cochrane central registers of controlled trial databases through July, 2018 and data were pooled using fixed effect modelling followed by random-effect methods (after assessing heterogeneity with fixed modelling). The primary outcome was the incidence of POST at 24 h after surgery/extubation. Comparative results were deliberated as pooled mean difference for continuous variables and Mantel–Haenszel (MH) odds ratio for dichotomous variables. Statistical analysis was done using Comprehensive Meta-Analysis-Version 3 (Biostat Inc., USA). **Results:** Seven trials involving 726 study participants were included in the final analysis. Incidence of POST at 24 hours was significantly lower in magnesium group (26/363) in comparison to active and non-active control group (89/363); $P = 0.00$- RR 0.22 (95%CI = 0.12-0.39, $I^2 = 0\%$). No significant adverse events were reported with the use of topical magnesium. **Conclusion:** Prophylactic use of topical magnesium before the induction of general anaesthesia seems to be an effective measure to decrease the incidence of POST.

Key words: Magnesium sulphate, meta-analysis, postoperative sore throat, systematic review, topical

INTRODUCTION

Post-operative sore throat (POST) is a common undesirable consequence of tracheal intubation. The prevalence of POST ranges from 21% to 65% after tracheal intubation varying in accordance with the mechanical trauma during intubation, tracheal tube cuff pressure leading to mucosal erosion, mucosal inflammation and dehydration.[1,2] In addition to a negative impact on patient satisfaction and recovery, POST increases the expenditure of health care.[3]

A number of non-pharmacological methods as well as pharmacological agents have been used to mitigate the condition. Non-pharmacological methods include use of supraglottic airway device instead of tracheal tube, smaller tubes, limiting cuff pressure and gentle oropharyngeal suctioning.[4,5] Various pharmacological

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agents like lignocaine, steroids and ketamine have been used with varying degree of success to reduce the incidence as well as severity of POST.[6-10]

Magnesium, an N-methyl-D-aspartate receptor antagonist found in central as well as peripheral nervous system, has anti-nociceptive and anti-inflammatory properties; therefore, it has been hypothesised to be useful for POST prevention.[11] Prophylactic efficacy of magnesium has been assessed by various randomised controlled trials showing controversial results.[12-19] To our knowledge, however, no systematic review has summarised the magnitude of their prophylactic efficacy from the numerous randomised trials published. Our group conducted this systematic review and meta-analysis of prospective randomised trials to study the efficacy of topical magnesium in preventing POST in adult patients undergoing surgery under general anaesthesia with single lumen tracheal tube.

METHODS

Cochrane collaboration methodology[20] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA[21] statement were followed for the conduct of our systematic meta-analysis. Following are the eligibility criteria.

Study type: Only randomised controlled trials were considered for enrolment.

Population: Publication on effect of administration of topical magnesium sulphate in the preoperative period on incidence of POST at 24 h in adult patients proceeding with surgery under general anaesthesia was included.

Intervention and comparators: Patients receiving magnesium sulphate as nebulisation/gargles were considered the intervention group. Non-active controls included normal saline or placebo, whereas active controls included the use of agents, such as aspirin and ketamine with a known impact on POST.

Outcome: The primary outcome was the incidence of POST in 24 h after surgery/extubation. Studies through inception to July 2018 were included in this meta-analysis. Our search included trials published in both English and non-English languages. Studies, which were published as letter to editor with incomplete data, were excluded.[12]

Data extraction

Comprehensive literature search was performed in PubMed, Google Scholar, EMBASE, Scopus and the Cochrane central registers of controlled trial databases through July 2018. Search terms 'postoperative sore throat', 'tracheal tube', 'magnesium', 'randomised clinical trial', 'adult' and 'severity' in various combinations were used. Parallel-group, randomised controlled design showing comparison of topical usage of magnesium sulphate with either non-analgesic or active control; recruiting adult patients undergoing surgery under general anaesthesia with single lumen tracheal tube disclosing the incidence and severity of POST 24 h after surgery/extubation were included in the meta-analysis. Search was extended to research articles published either as full manuscripts or abstracts of meeting in peer-reviewed journals. References of comparable meta-analysis were also searched manually for relevant trials. Our search included trials published in both English and non-English languages. Once the abstract was analysed by the searching reviewer and found appropriate, full text of the article was further studied.

Two authors (NPS and JKM) independently reviewed all articles and relevant articles were selected. Disagreements were resolved through discussion and in case of any disagreement, PMS was consulted. NPS and JKM independently extracted data pertaining to demographic profile of the patients; year and country of trial, surgery performed; size of tracheal tube, tracheal cuff pressure, duration of intubation, interventions used, incidence of POST at various time intervals, severity of POST, cough and post-operative hoarseness. Duplicates obtained from individual search by different reviewers were identified and were removed using Endnote (Thompson Reuters, USA). Data were abstracted into a standardised format entered into Microsoft Excel 2016 (Microsoft Corporation, USA). Cross-references of relevant articles were then searched to ensure enrolment of all eligible studies.

Assessment of bias and quality of evidence

Risk of bias was assessed using the Cochrane risk of bias assessment tool.[20] Each randomised trial was assessed based upon seven domains of potential bias (random sequence generation, allocation concealment, blinding of intervention, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias). The overall risk of bias of individual studies was classified as high-risk if at least two domains were determined at high-risk or if there were more than

two domains of unclear risk, moderate risk if at least two domains were determined at unclear risk, and low risk if all the domains were determined at low risk. The grading of recommendations, assessment, development and evaluation (GRADE) system was used to assess quality of evidence as high, moderate, low or very low.[22]

Outcome measures and statistical analysis

The primary outcome was the incidence of POST in 24 h after surgery/extubation. Incidence of POST at 6 h, and severity of POST were the secondary outcomes analysed. The Mantel–Haenszel (MH) odds ratio (OR) was calculated for dichotomous outcomes and standardised mean differences for continuous outcomes. Data were presented with the corresponding 95% confidence interval (CI). In case data were presented as median with interquartile range, method proposed by Wan *et al*.[23] was used to convert the values to mean and standard deviation. Statistical heterogeneity was tested using the I^2[24] and Q statistics Egger's method[25] was used to assess small study effect or publication bias. Values of $I^2 < 40\%$, 40%–60%, 60%–90% were considered non-significant, moderate heterogeneity and high heterogeneity, respectively.[24]

Primary analyses were performed pooling both non-active and active (analgesic) controls. In case a trial had more than one arm of intervention, control arm was considered separately with comparator (magnesium) for primary analysis.

Comprehensive Meta-Analysis-Version 3 (Biostat Inc., USA) was used for the statistical analysis. Fixed effect modelling followed by with random-effect methods (after assessing heterogeneity with fixed modelling) was used for performing the meta-analysis. Comparative results were deliberated as pooled mean difference for continuous variables and Mantel–Haenszel (MH) OR for dichotomous variables. $P < 0.05$ was deemed statistically significant. 'Fixed effect modelling' were used when heterogeneity was found to be lower than 40% otherwise results from random effect modelling are presented. Egger's regression test was used to quantify publication bias and was further judged by the usage of funnel plot.

RESULTS

Literature search

Initial search yielded 199 titles and abstracts. A total of 7 trials involving 726 study participants were included in the final analysis. The process of screening and inclusion of RCTs is shown in Figure 1. One trial by Gupta *et al*.[12] evaluated the efficacy of nebulised magnesium sulphate for attenuating POST. Though authors reported decrease in incidence and severity of POST till 24 h, actual data were not reported in this letter to editor.

Study characteristics [Table 1]

All the authors monitored the cuff pressure and kept it below 25–30 cm of H_2O throughout the study duration. Reported tube size was also fairly constant across all the trials. All the female participant's tracheas were intubated with tubes of outer diameter 7–7.5 mm and 8–8.5 mm size was used for male patients. Duration of tracheal intubation was reported by most of the authors and it ranged from 51 to 120 min.

Only one trial[16] included participants undergoing emergency surgery (i.e., acute appendicitis) and the rest of the trials enrolled elective surgeries, such as spine, abdominal and orthopaedic procedures.[13-16,17-19] Magnesium was given through topical routes, namely, nebulisation in four trials,[13,15,18,19] gargles in two studies[14,16] and lozenges[17] was used in one trial. Nebulisation dose of magnesium ranged from 225 to 250 mg; 20 mg/kg was given through gargling across the trials and 100-mg lozenges were used. Non-analgesic controls were normal saline in four trials and placebo in one trial. The comparator agent with known analgesic was ketamine in three trials[13,16,19] and aspirin in one trial.[14] Information on characteristics of patient, anaesthetic techniques, surgical procedures and number of interventions are listed in Table 1. Trial by Rajan *et al*. and Jain *et al*. compared three groups (two active and one control) as the values of individual groups were reported separately; we were able to obtain two comparisons for pooled results from both these studies. These comparison arms are labelled as (1) and (2) for better reader comprehension and to avoid group identification confusion.

In one trial, the study participants were in prone position for surgery;[18] in three trials, surgery was undertaken with patients in supine position[13,16,19] and the remaining three studies did not mention the surgical position.[14,15,17] Only one trial used succinylcholine as muscle relaxant for intubation,[16] whereas the rest of the researchers used non-depolarizing muscle relaxants.

The study participant's mean age was 37.14 ± 10.66 in control group and 36.86 ± 10.22 in comparator

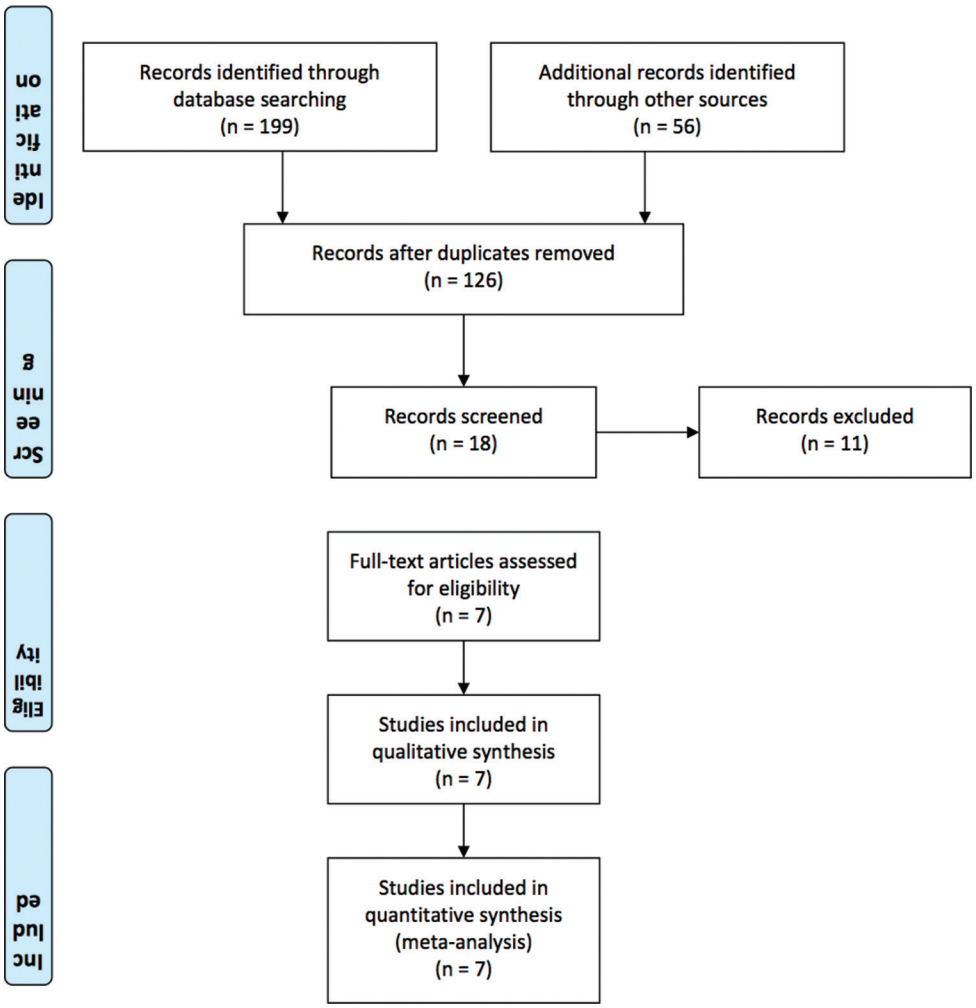

Figure 1: Flowchart showing selection of RCT for meta-analysis

group. One group of researchers enrolled only female participants,[19] one group did not report patient's gender,[13] but others enrolled subjects of either sex.[14-18] Control and treatment groups in the reported trials had comparable distribution of genders. Six trials included patients with ASA physical status 1–2,[14-19] whereas only one trial included patients with ASA physical status 1–3.[19]

Study quality assessment

Figure 2 shows the methodological qualities of selected studies. Methods of allocation generation were described in four trials,[13,14,17,19] and two studies provided the detailed methods of allocation concealment.[17-19] Four studies provided detailed information regarding the blinding of patients as well as assessors.[13,14,17,19]

Primary outcome

Data of sore throat 24 h postoperatively were available in 7 trials that included 363 patients in control and 363 patients in the comparator group. Incidence of POST was significantly lower in comparator group (26/363) in comparison to control group (89/363); $P = 0.00$, RR 0.22 (95% CI = 0.12–0.39 $I^2 = 0\%$) [Figure 3]. All these seven trials reporting the primary outcome were also further sub-grouped based upon the use of non-active control. On subgroup analysis, incidence of POST was significantly lower in the comparator group (12/220) as compared to the non-active control group (57/220); $P = 0.00$. RR 95% CI 0.18 (0.09–0.36). Four trials used known analgesic agents as comparator. The active comparator was ketamine in three trials and aspirin in one trial. When compared with ketamine or aspirin, there was no statistically significant difference in the incidence of sore throat with use of magnesium.

Topical magnesium reduced the severity of POST by nearly 78% as compared to the control group at 24 h after surgery. The number needed to treat for reduction of one episode of sore throat with the use

Table 1: Characteristics of studies included

Author/ country	Sample size (F%)	Age	Duration of surgery/ anaesthesia (min)	Post-op analgesia	Intervention	Tracheal tube (F)	Cuff pressure (cm H_2O)
Borazan (2012) Turkey[17]	70 (30)	18-50	84±12 86±9	Tramadol	1. Magnesium-Diasporal lozenge containing 100 mg magnesium 2. Placebo lozenges	8.5 (7.5)	20-22
Chattopadhya (2016) India[14]	56 (25)	18-50	50.4±6.9 53.3±7.3	PCM	1. Gargling with 20 mg/kg magnesium sulfate solution dissolved into 20 mL of 5% dextrose solution 2. Gargling with 325 mg tablet dissolved into 20 mL of 5% dextrose solution	8-9 (7-8)	18-20
Jain (2017) India[19]	150 (100)	20-50	<120	PCM & Tramadol	1. Nebulisation with 3 ml of 225 mg isotonic magnesium sulfate 2. Nebulisation with 3 ml solution containing 50 mg ketamine 3. Nebulisation with 3 ml normal saline	(7-7.5)	20
Rajan (2017) India[13]	60 (NR)	18-80	comparable	Epidural	1. Nebulisation with 5 ml solution containing 250 mg magnesium 2. Nebulisation with 5 ml solution containing 500 mg magnesium 3. Nebulisation with 5 ml solution containing 50 mg ketamine 4. Nebulisation with 5 ml solution containing normal saline	8-8.5 (7-7.5)	20-25
Sharma (2017) India[18]	140 (30)	25-50	127.8±9.7 131.4±8.2	Diclofenac	1. Nebulisation with magnesium sulfate 225 mg 1 ml with 4.0 ml of normal saline 2. Nebulisation with 5 ml normal saline	8-8.5 (7-7.5)	10-20
Teymourian (2015) Iran[16]	100 (46)	25-75	52.5±23.4 55.8±21.2	NM	1. Gargling with 20 mg/kg magnesium sulfate in 30 mL 20% dextrose water 2. Gargling with 0.5 mg/kg ketamine in 30 mL 20% dextrose water	NM	20-30
Yadav (2016) India[15]	100 (47)	18-60	approx. 120	NM	1. Nebulisation with 3 ml of 225 mg isotonic magnesium sulfate 2. Nebulisation with 3 ml of normal saline	8 (7)	20

NM – Not mentioned, PCM – Paracetamol

of magnesium was 5.76. This comparison had 'zero' overall heterogeneity.

Secondary outcomes

Incidence of early sore throat

Sore throat at 6 h: The incidence of sore throat at 6 h was available in all the seven trials. Incidence of sore throat was significantly lower in the comparator group 66/363 in comparison to the control group 141/363; $P < 0.001$, RR 0.22 (95%CI = 0.14–0.34 I^2 = 68.31%, random effects) [Figure 4]. This amounted to a reduction of 78% in the incidence of sore throat in comparison to the control group. Number needed to treat (NNT) for prevention of single episode of early sore throat with the use of magnesium was 4.84. Grade quality of evidence was judged to be high.

We performed a sensitivity analysis using 'single study removal method' to explore for the high heterogeneity for this variable. The study by Rajan *et al*. contributed highly to the heterogeneity and on excluding ketamine arm of the trial, the heterogeneity dropped to 49.14%.

Severity of sore throat

Six trials provided information on severity of sore throat. None of the patients developed severe sore throat in any of the studies.

Mild severity: The incidence of mild sore throat was disclosed in six trials. The overall incidence of mild sore throat was 12/248 in the magnesium group compared to 28/248 in the control group. The MH OR for mild sore throat with the usage of magnesium was 0.43 (95%CI being 0.21–0.87) [P = 0.02, I^2 = 0%] [Figure 5]. This amounted to nearly 57% reduction in incidence of mild sore throat with the use of magnesium with an NNT of 15.50. Grade quality of evidence was judged to be moderate.

Moderate sore throat: This variable was reported by 5 trials that included 213 patients each in magnesium and control groups. Incidence of moderate sore throat

was 0.04% and 9.38% with magnesium and control, respectively. The MH OR for sore throat with usage of magnesium as compared to control was 0.15 (95%CI being 0.05–0.5), [P = 0.00, I^2 = 0%] [Figure 6].

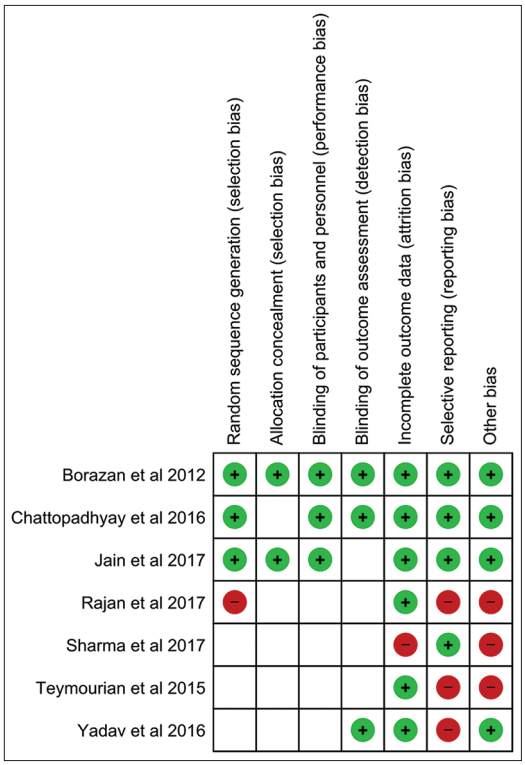

Figure 2: Risk of bias summary

Magnesium led to reduction of moderate degree of sore throat by around 85% over control group with an NNT of 11.21.

Comparison with ketamine: Magnesium usage was found to be comparable to topical ketamine, reported in 3 trials with 230 patients in preventing sore throat at 24 h, MH OR was 0.53 (95%CI being 0.14–1.97) [P = 0.34].

Only four studies commented on incidence of hoarseness and cough at 24 h. No cough or hoarseness was found at 24 h in three studies and in one trial only one patient had hoarseness at 24 h.[14] Three trials reported the information on adverse events associated with study drug.

Publication bias

Both funnel plot and Egger's regression test were used to evaluate for the publication bias in 24-h incidence of sore throat (primary variable). There was a symmetrical distribution of trials on Funnel plot. Egger's test demonstrated an X-axis intercept at 0.096 with P values of 0.916 (two-tailed) [Figure 7]. Both these indicated that the publication bias was unlikely.

DISCUSSION

We conducted this meta-analysis to assess the efficacy of topical magnesium in preventing POST in adult

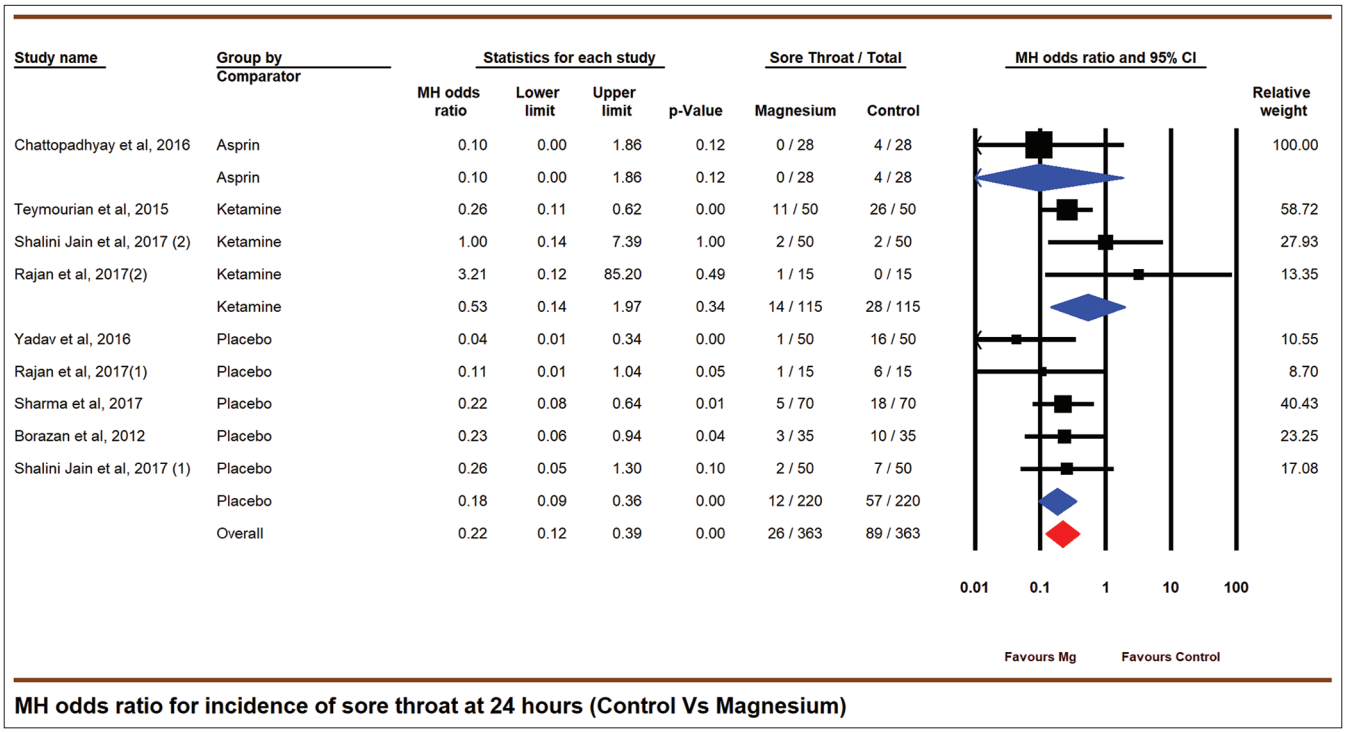

Figure 3: Forest plot showing comparison of magnesium with control in 24 h

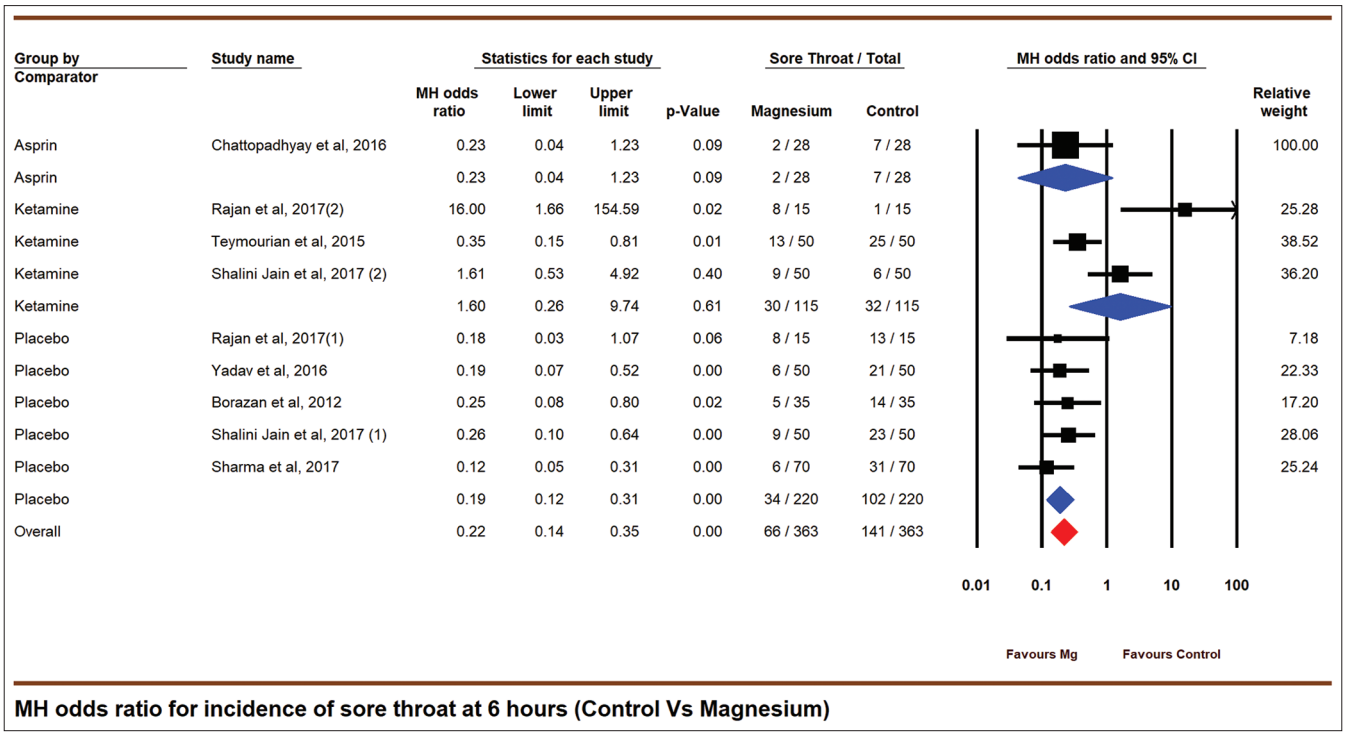

Figure 4: Forest plot showing comparison of magnesium with control at 6 h

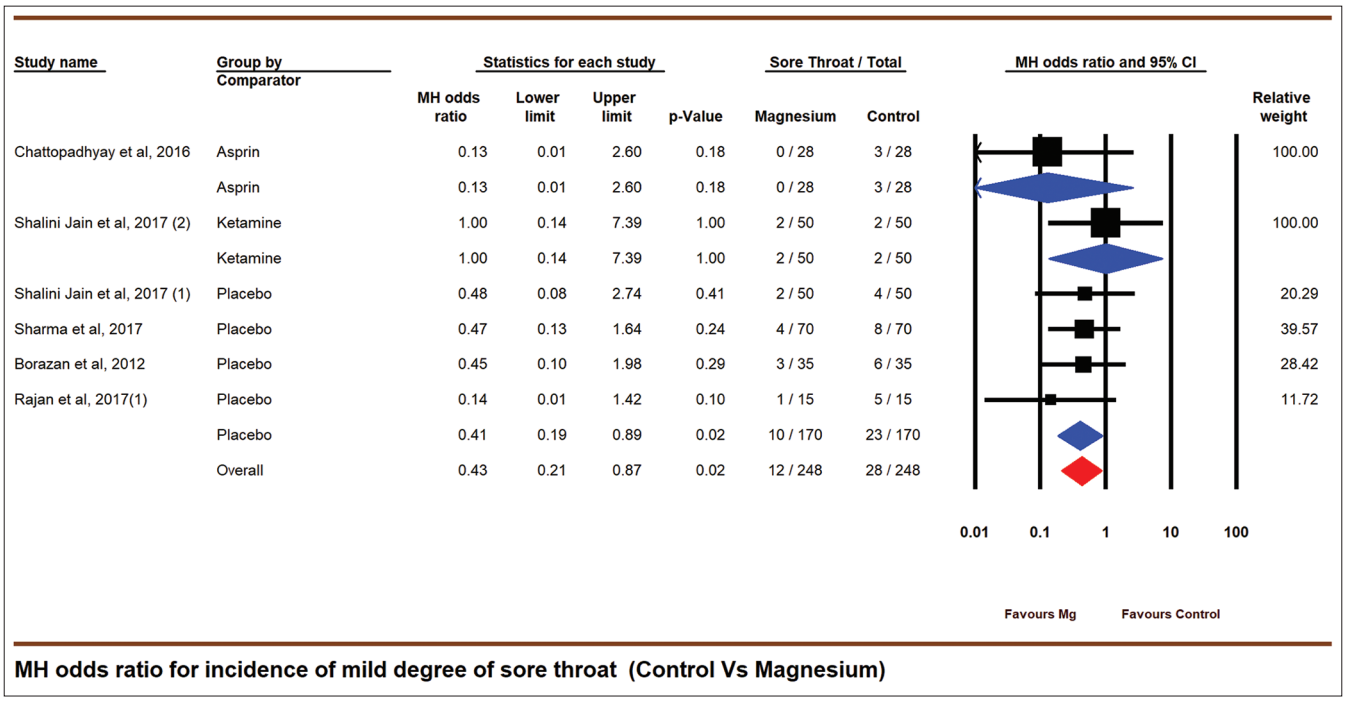

Figure 5: Forest plot depicting incidence of mild sore throat for magnesium and control at 24 h

patients undergoing surgery with general anaesthesia and oral intubation. We found that magnesium is an effective agent to reduce the incidence of POST. Prophylactic use of magnesium against POST is also associated with a reduction in severity of this undesirable post-operative complication.

POST is a minor but distressing post-operative complication. Only a limited number of research articles on airway complications have studied POST, even though it hampers the patient's recovery and potential increased health care cost.[26-28] In this systematic review, use of magnesium was

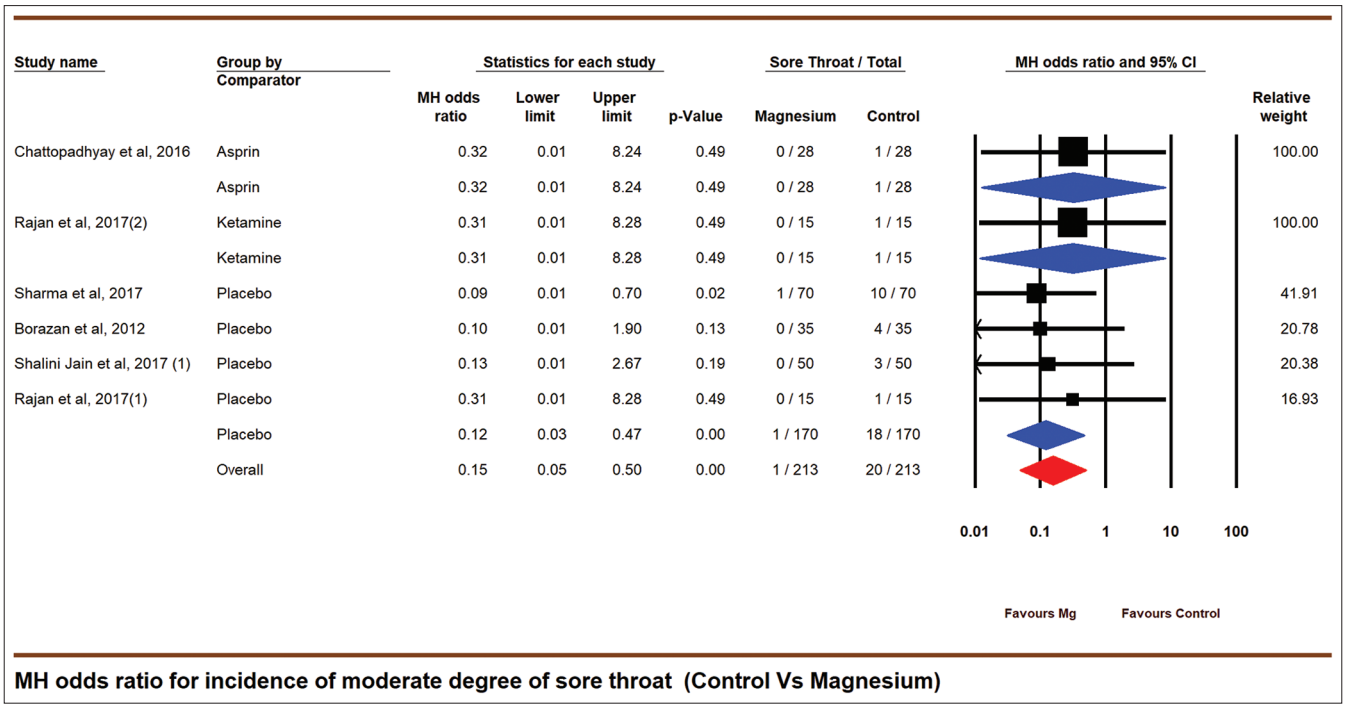

Figure 6: Forest plot showing incidence of moderate sore throat for magnesium and control at 24 h

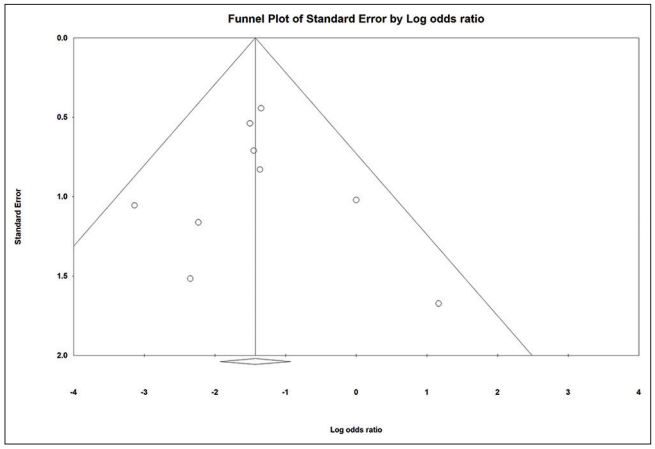

Figure 7: Funnel plot of standard error

associated with significant reduction in incidence of sore throat during the first 24 h after surgery in comparison with placebo group without any significant adverse effect documented. The number needed to prevent POST when using magnesium was 5.76 indicating a large prophylactic effect. Grade quality of evidence for incidence of POST reduction with use of magnesium was high. Use of this drug reduced the severity of POST by nearly 78%. Among the deleterious outcomes secondary to POST in patients, the most important are delayed discharge, discomfort and even dangerous sympathetic response. However, we were not able to measure the effect of magnesium on these POST-related outcomes because of the lack of information in the trials included.

The trigger of POST is usually pharyngolaryngeal mucosal inflammation secondary to localised trauma inflicted by cuff of tracheal tube. Therefore, a high number of anti-inflammatory agents have been proposed to be effective in reducing POST.[29-32] Tanaka *et al*., in their meta-analysis reported positive results with lignocaine that were dependent on study quality; drug concentration; route of administration and management of cuff pressure during anaesthesia.[33] Administration of ketamine gargle prior to induction of general anaesthesia with airway instrumentation was found to improve patient satisfaction by decreasing patient discomfort and the need for adjunct pain therapy in a meta-analysis conducted by Mayhood *et al*.[34] Corticosteroids applied to tracheal tubes were superior both to non-analgesic controls and lignocaine, in preventing POST in a meta-analysis conducted by Kuriyama *et al*.[35] Same group of authors conducted another meta-analysis to assess the efficacy and safety of topical application of benzydamine to prevent POST in adults undergoing elective surgery under general anaesthesia.[36] Authors found that benzydamine was also associated with a reduced incidence of POST when compared with lignocaine. However, the effects of benzydamine hydrochloride on the incidence of POST have only been compared in small trials.

Consolidated standards of reporting trials (CONSORT) statement requires trial investigators to report on harms associated with interventions.[37] Though all seven trials were published after publication of this statement; four trials did not report adverse effects of their intervention.[14,16,18,19] Our analysis of the limited evidence available suggests that topical use of magnesium is not associated with greater incidence of adverse events. As for the potential side effects of topical magnesium like gastric irritation, diarrhoea or nausea were noted in one trial[17] and author did not observe any of these side effects. Other three studies[14,15,18] did not define the side effects they had noticed. However, they reported absence of any adverse effects.

Magnesium was administered as gargles, lozenges or nebulisation 15–30 min before surgery in preoperative area. Only one study defined the size of droplets produced by the nebuliser. Jain *et al*. used nebuliser that produced droplets of size 5–8 microns resulting in only 37%–60% of the drug getting deposited in oropharynx. Nebulisation ensures that the drug is equally and effectively distributed all over the pharynx and up to the beginning of the respiratory tract. In addition, nebulisation prevents the user variability associated with gargling and confounded the issue of taste of the medications.[19] Lozenges used allow immediate release of the drug, which adheres to the pharyngeal wall and decreases the oedema. Further magnesium thus released has local analgesic and anti-inflammatory effects, especially in the presence of alkaline pH, in which magnesium is highly concentrated in inflamed tissue and has minimal systemic absorption. This prolongs the action and decreases possibility of side effects.[17]

One of the strengths of our meta-analysis was that greater proportion of enrolled randomised controlled trials used a similar route of administration and dose of magnesium. Furthermore, our analysis showed no heterogeneity. In addition to incidence of POST, we were also able to define the effect of magnesium on severity of POST as five out of seven trials had data pertaining to severity also. Third, we used the Cochrane methodology when performing this systematic review. Quality of evidence was assessed using the GRADE criteria. We further confirmed the robustness of our findings using sub-group sensitivity and trial sequential analyses.

There are few limitations of this meta-analysis. First, the minimum dose of magnesium required for optimal effect could not be defined as most of the studies used similar doses. Second, only the effect of magnesium as compared to placebo could be studied because of the limited number of studies comparing magnesium with active control. Though our results suggest that topical magnesium is associated with reduced sore throat, our study was not able to prove whether it is better than or equivalent to other agents like lignocaine, corticosteroids or ketamine. We could not perform a meta-regression analysis because of limited number of studies. We could not adjust for variables like higher cuff pressure and larger tracheal tubes size, which are known risk factors for POST. Additionally, as only four trials collected the data on adverse events associated with magnesium, we could not assess the safety of the drug. Publication bias is present in some outcomes despite our comprehensive search

CONCLUSION

Prophylactic topical magnesium, before the induction of general anaesthesia, seems to be an effective measure to decrease the incidence of POST. We encourage the use of this agent in clinical practice and suggest further studies that assess the impact of magnesium on patient's recovery and the cost-effectiveness of this strategy.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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