Efficacy of topical agents for prevention of postoperative sore throat after single lumen tracheal intubation: a Bayesian network meta-analysis

Efficacité des agents topiques pour la prévention des maux de gorge postopératoires après une intubation avec tube endotrachéal simple lumière : une méta-analyse bayésienne en réseau

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Abstract

Background The optimal choice of prophylactic drugs to decrease postoperative sore throat is unclear. The objective of this network meta-analysis (NMA) was to compare and rank 11 topical agents used to prevent postoperative sore throat.

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Methods Various databases were searched independently for randomized-controlled trials (RCTs) comparing topical agents used for the prevention of postoperative sore throat. Inclusion criteria were parallel group studies comparing intervention with active or inactive control and reporting postoperative sore throat. The primary outcome was postoperative sore throat at 24 hr. Secondary outcomes were early sore throat at 4–6 hr, cough, and hoarseness at 24 hr.

Results Evidence was synthesized from 70 RCTs reporting 7,141 patients. Topical application of lidocaine, corticosteroids, ketamine, magnesium, benzydamine, water-based lubricant, and liquorice applied along the tracheal tube, to the tracheal tube cuff, gargled or sprayed were compared with intracuff air and each other. Bayesian NMA showed that magnesium (odds ratio [OR], 0.10; 95% credible interval [CrI], 0.03 to 0.26), liquorice (OR, 0.14; 95% CrI, 0.03 to 0.55), and steroid application (OR, 0.11; 95% CrI, 0.06 to 0.22) most effectively prevented postoperative sore throat at 24 hr. Topical lidocaine was the least effective intervention.

Conclusion Topical application of magnesium followed by liquorice and corticosteroids most effectively prevented postoperative sore throat 24 hr after endotracheal intubation.

Résumé

Contexte Le choix optimal des médicaments prophylactiques pour réduire les maux de gorge postopératoires n'est pas clair. L'objectif de cette méta-

analyse en réseau (NMA) était de comparer et classer 11 agents topiques utilisés pour prévenir les maux de gorge postopératoires.

Méthode Des recherches ont été réalisées dans plusieurs bases de données de façon indépendante afin d'en extraire les études randomisées contrôlées (ERC) comparant des agents topiques utilisés pour la prévention des maux de gorge postopératoires. Nos critères d'inclusion étaient des études de groupes parallèles comparant une intervention à un témoin actif ou inactif sur des résultats de maux de gorge postopératoires. Le critère d'évaluation principal était les maux de gorge postopératoires à 24 h. Les critères d'évaluation secondaires comprenaient les maux de gorge précoces à 4-6 h, la toux et l'enrouement à 24 h.

Résultats Les données probantes ont été synthétisées à partir de 70 ERC portant sur 7141 patients. L'application topique de lidocaïne, de corticostéroïdes, de kétamine, de magnésium, de benzydamine, d'un lubrifiant à base d'eau et de la réglisse, appliqués le long du tube endotrachéal, sur le ballonnet du tube endotrachéal, en gargarisme ou en vaporisation, ont été comparées à l'air intra-ballonnet et entre les divers agents. La NMA bayésienne a démontré que l'application de magnésium (rapport de cotes [RC], 0,10; intervalle de crédibilité [CrI] 95 %, 0,03 à 0,26), de réglisse (RC, 0,14; CrI 95 %, 0,03 à 0,55) et de stéroïdes (RC, 0,11; CrI 95 %, 0,06 à 0,22) étaient les méthodes plus efficaces pour prévenir les maux de gorge postopératoires à 24 h. La lidocaïne topique était l'intervention la moins efficace à 24 h.

Conclusion L'application topique de magnésium, suivie de celle de réglisse et de corticostéroïdes, est l'approche qui prévient le plus efficacement les maux de gorge postopératoires 24 h après une intubation endotrachéale.

Keywords Postoperative sore throat prophylaxis · Cough · Hoarseness · topical agent · tracheal tube

Postoperative sore throat is common after general anesthesia and tracheal intubation with an incidence ranging from 21% to 68%.^{1,2} Postoperative sore throat is the second most common adverse outcome following a general anesthetic and negatively impacts patient satisfaction.²⁻⁴ Postoperative sore throat is difficult to treat, even when the operative pain has been controlled by administration of systemic analgesic medications.⁵ Furthermore, anesthesiologists may not be aware of the incidence of sore throat in their own practice, as many patients may not seek medical advice for postoperative sore throat.⁶ Thus, although a minor complication, attenuation of the symptoms of sore throat in the postoperative period is a worthwhile goal.

The potential mechanisms of sore throat are thought to be irritation, mechanical trauma, and inflammation secondary to insertion of endotracheal tube (ETT) and inflation of the cuff.^{2-4,7} Various non-pharmacologic and pharmacologic measures have been used prophylactically to reduce the risk of this postoperative complication. Non-pharmacologic methods include using a supraglottic airway device instead of a tracheal tube, using a smaller tube, limiting cuff pressure, and using gentle oropharyngeal suctioning.^{2,4} Topical application of various pharmacologic agents including lidocaine, corticosteroids, ketamine, magnesium, and benzydamine has been utilized to varying degree of success. Topical application of non-drug compounds such as water-based lubricant and liquorice has been examined. A variety of routes of application have been explored including nebulization, gargling, and direct application of the agent to the ETT cuff. Inhalation of corticosteroids from metered-dose inhalers or spacer device and inflation of the tracheal tube cuff with local anesthetics and saline have also been evaluated. Yet, given the variety of different agents available, the optimal choice of agent remains unclear. Previous attempts to synthesize existing data have been limited to pairwise meta-analyses and do not provide a comprehensive enough evaluation of the evidence to make an efficacious choice.⁸⁻¹¹ The selection of prophylactic agent, therefore, is still influenced by clinical dogma, convenience, or institutional availability.

To address this shortcoming, we performed a network meta-analysis (NMA) to pool and analyze data from randomized-controlled trials (RCTs) comparing various topical agents used for prophylaxis of sore throat in adult patients undergoing surgery with tracheal tube general anesthesia. Treatments were rank-ordered from most to least effective to guide clinicians.

Methods

The systematic review followed by NMA was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Network Meta-analysis (PRISMA) guidelines.¹² The review protocol was registered with PROSPERO (registration number CRD42018116448) on 29 November 2018.

Two independent reviewers (N.S. and J.M.) performed a comprehensive literature search of PubMed, Google Scholar, EMBASE, and the Cochrane central registers of controlled trial databases for abstracts, conference proceedings, and full text papers that evaluated agents used to prevent postoperative sore throat from the date of inception to 31 October 2018. To identify additional references, reviewers also hand-searched meta-analyses

and systematic reviews and guidelines published on this topic. Our search strategy is outlined in the electronic supplement. The search was run to retrieve the relevant articles according to standard population, intervention, comparison, outcome, timing, and study design (PICOTS) criteria as follows: adult anesthesia (population), various drugs (intervention and comparison), sore throat (outcome), 24 hr (timing), randomized-controlled trial (study design), and postoperative period (setting). Free text and MeSH terms were used individually, and in various combinations, then cross-references of articles were searched to ensure identification of all eligible studies. We placed no restriction on the language of manuscripts included.

Inclusion criteria

- Population: adults between the age of 18 and 75 yr.
- Interventions: preventive, topical application of one of the following treatments in the preoperative period among adult patients undergoing surgery under general anesthesia with single lumen tube: lidocaine, corticosteroid, ketamine, magnesium, benzydamine, water-based lubricant, and liquorice. Inhaled corticosteroids and inflation of the ETT cuff with lidocaine and 0.9% saline were also included.
- Comparator: active or non-active control (most commonly intracuff air).
- Outcome: sore throat.
- Study design: prospective, parallel, RCTs.
- Timing: 24 hr.
- Setting: postoperative period

Exclusion criteria

- Studies conducted with double lumen tube.
- Trials examining different strategies for administration of same agent.

Information source

STUDY SELECTION

Two investigators (N.S. and J.M.) independently reviewed and assessed the eligibility of studies and abstracts that were deemed eligible after review of their full text. Any discrepancies on inclusion of a trial in our final analysis were initially resolved by discussion or by harmonisation by a third independent author (P.S.).

DATA EXTRACTION

Two reviewers (N.S. and J.M.) independently extracted the data from each included manuscript using a predefined data extraction form, which was specifically designed by the review group. The following items were extracted: the trial setting (country, year of publication), participants (sample size, age, and sex), type of surgery (laparoscopy, gynecologic, orthopedics, etc.), prophylaxis (drug, dose, route and timing of administration), study design, and outcome measures. Any disagreement concerning the extracted data were resolved by discussion. Study authors were contacted in case of missing or unclear information.

DATA ITEMS

The primary outcome was the sore throat at 24 hr following extubation. Secondary outcomes included: 1) early (4–6 hr) sore throat; 2) cough at 24 hr; and 3) hoarseness at 24 hr. A four-level grading system has been used in literature to rate the severity of the postoperative sore throat: none, mild, moderate, and severe. We used the sum of mild, moderate, and severe cases to calculate the occurrence of sore throat.

We clustered similar pharmacologic agents to organize interventions (e.g., topical applications of any corticosteroid preparations were pooled). We clustered modes of application of a given agent including gargling, nebulization, spray, and coating of the ETT cuff gel. Inhalation of corticosteroids and intracuff application of lidocaine (either non-alkalinized or alkalinized) and saline were considered separately from one another and other agents.

Risk of bias (ROB) assessment

Two independent reviewers manually reviewed all publications. Risk of bias was assessed based upon the criteria recommended by the Cochrane Collaboration (ROB2).¹³ This tool evaluates the ROB according to five domains: bias arising from the randomization process, bias due to deviation from intended interventions, bias due to missing data outcomes, bias in measurement of outcome, and bias in selection of reported results. The overall ROB was expressed as low risk, some concerns, or high risk. Publication bias was visually inspected using the funnel plot.

*Grading the quality of evidence*¹⁴

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool was used to evaluate the quality of the evidence and make recommendations. Each outcome was assessed as high,

moderate, low, and very low evidence value, depending on the design of the studies, ROB, inconsistency, indirect evidence, imprecision, and publication bias.

Statistical analysis

An NMA evaluates treatments (nodes) based upon three assumptions. “Exchangeability” assumes that included trials have very similar methodology and inclusion criterion and compare similar interventions. To uphold this, we only included RCTs with similar methodology evaluating sore throat. “Homogeneity” is an idealistic assumption that assumes there is no heterogeneity (or no diversity) across trials. In an NMA, this variation can be quantified as “heterogeneity” across each direct (pairwise comparison). The third assumption that is unique for a network analysis is “transitivity”. Absolute transitivity is yet another idealistic assumption. It suggests that there is no relevant discrepancy or inconsistency between direct and indirect evidence. Deviation from transitivity in a network is measured as network “inconsistency”. We evaluated this parameter in our network using net-heat and node split method. The node-splitting approach is especially attractive because inconsistency is evaluated one comparison at a time by separating the direct evidence on that comparison from the network of indirect evidence. The discrepancy between the estimates of relative treatment effects from these two sets of trials indicates the level of inconsistency. We used a Bayesian method because Bayesian inference via Markov Chain Monte Carlo (MCMC) modelling is unbiased with respect to sample size and can accommodate any sample size no matter how small.¹⁵ Frequentist inference, in contrast, becomes more biased as sample size decreases and is often wildly biased with small samples. We also planned to perform meta-regression for study level data in “Gemtc”, which is Bayesian-based modelling.

For each trial, the probability of postoperative sore throat was analyzed and expressed as the odds ratio (OR) with 95% credible interval (CrI) and whenever possible results were used from an intention-to-treat population. After extraction of required data, the evidence patterns shown by the network plot were examined to ensure that a closed network was formed by all preventive strategies and all nodes were included in the network. The pairwise association between each agent (also called the “direct estimate”) was depicted by a graphical representation of the network. In the diagram, each preventive modality is represented by a node and the edge connects the agents that have been directly compared in one or more RCTs.

The Bayesian network analysis was carried out by modelling the postoperative sore throat with the Bayesian hierarchical model (binomial model with logit link

function) using the MCMC approach. The Gemtc package uses vague priors [normal (0, 0.0001)] for estimating the trial baselines, treatment differences, and the random-effects standard deviation [uniform (0,)]. We ran 5,000 adaptations and 20,000 iterations with a thinning factor of 10. These parameters helped us to get a potential scale reduction factor of less than 1.05.

We used residual disseminated intravascular coagulation (DIC) comparing both random and fixed effects, which is shown in the Electronic Supplementary Material (ESM) eTable. The model constructed for evaluating DIC had 158 data points. The DIC value was 414 for the fixed effect model and 291.1 for the random effect model. The closer the DIC is to the model data points, the better the model fit. Thus, we used random-effects model for our reporting. The results from the random-effects model are presented as ORs with 95% CrI. The Bayesian concept uses the CrI, which is a more practical concept than the confidence interval because indirect effects introduce some degree of uncertainty in pooled outcomes. For a 95% CrI, the value of interest (e.g., size of treatment effect) lies with a 95% probability in the interval. Unlike the confidence interval, which defines boundaries for point estimate values, the CrI defines boundaries for probability values. Lastly, the probability was calculated to be the first, the second, the third, and the worst agent and is represented in the correspondent rank order of preference.

R assisted by package “gemtc” (R repository, Comprehensive R Archive Network) was used for statistical analysis. The MCMC modelling was performed using a Gibbs sampler. For the construction of network diagram and net-heat plot, the “netmeta” package was used in R.

Exploration of heterogeneity

Network meta-analysis assumes that trials are homogeneous in measures of effect size, and generate estimates for direct and, more importantly, indirect comparisons. In reality, this assumption is rarely entirely valid because of inevitable variation in study procedures and populations. We evaluated model inconsistency using the DIC values and overall deviance for each parameter analyzed. The lower the DIC values compared with the estimated number of data points, the lower the inconsistency. We made a net-heat plot to visually inspect and locate sites of high inconsistency in our network. Further, we used a node-splitting approach to quantify variations between direct and indirect estimates at each node.

Results

Characteristics of included studies

We identified 2,986 references and reviewed 312 full-text manuscripts. A total of 70 trials were included in the final analysis.^{5,16–84} The number of studies identified at each step are reported in the PRISMA diagram (Fig. 1). Two non-English trials were included in the final analysis.^{46,63} No conference meeting abstract provided complete data that met inclusion criteria. Key information of the 70 included studies is presented in the eTable (ESM). The included studies reported the postoperative sore throat at 24 hr in a total of 7,141 participants. Multiple groups were common among the included trials: one trial reported six groups,⁸⁰ four trials reported four groups,^{24,38,40,55} and 19 trials reported three arms.^{16,17,23,25–27,32,39,41,45,46,48,52,53,56,62,67,72,81} The remaining 44 trials were simple two-arm comparisons.

Included trials were reported between 1997 and 2018 and were relatively homogeneous with regard to age, sex, intubation times, and type of surgeries within groups. Early (4–6 hr) sore throat was reported in 42 trials comprising 4,813 participants with eight comparative agents. The incidence of cough at 24 hr was analyzed in 23 trials including 2,405 patients with ten different agents. The incidence of hoarseness at 24 hr was studied in 24 trials with 2,600 participants employing ten active agents.

Summary of network geometry

All networks were complete, as all the nodes could be connected. The network geometry across outcomes showed a preponderance of studies comparing topical ketamine and topical steroids with the intracuff air (Fig. 2). Overall, 107 possible pairwise comparisons could be made between the 11 treatments for incidence of sore throat at 24 hr. Of these,

Fig. 1 PRISMA flow diagram of included randomized-controlled trials.

Fig. 2 Network plot showing the network geometry for postoperative sore throat at 24 hr. Size of nodes corresponds to sample size of treatment group (reported in parentheses). Lines connecting the nodes show the number of trials (in parentheses) comparing the connected nodes and is proportional to the thickness of line. Benz = benzydamine; IcAr = intracuff air; IcLi = intracuff lidocaine; IcNS = intracuff normal saline; IhSt = inhaled steroid; Keta = ketamine; KYJe = water-based lubricant; Lido = lidocaine; Liqr = liquorice; Mg = magnesium; Ster = corticosteroid.

22 comparisons were formed directly by head to head evidence, but five of the direct connections had only one trial. Several comparisons had been directly studied in one or more trials of which lidocaine ($n = 33$), steroids ($n = 24$), and ketamine ($n = 22$) had the most links. The most common comparison ($n = 17$) was between ketamine and intracuff air. Network graphs and other results for secondary outcomes are discussed in subsequent sections. We noted that all secondary outcomes displayed geometry similar to the sore throat at 24 hr and we were able to connect all the treatment nodes in all other secondary interventions.

Outcome parameters

Sore throat at 24 hr

The complete network diagram with total number of patients included in each group is shown in Fig. 2. The comparative OR for sore throat at 24 hr with all the included agents is shown in Table 1. The rank order of preference is shown in eFig. 1 (ESM) and represents the probability of each drug occupying a given ranking. The

combined probability of magnesium (OR, 0.10; 95% CrI, 0.03 to 0.26, ranked first) and liquorice (OR, 0.14; 95% CrI, 0.03 to 0.55, ranked second) for being the “best” treatment was found to be more than 55%, corticosteroid application (OR, 0.11; 95% CrI, 0.06 to 0.22) followed them and was ranked third. Use of magnesium was associated with the lowest incidence of sore throat. The results were reported for the random-effects modelling and the DIC for this model was 291.97 (with 158 data points and a residual deviance of 165.4). Network inconsistency for sore throat was estimated based upon a net-heat plot (eFig. 2; ESM).

Risk of bias

Figure 3 presents ROB assessment of the studies for sore throat at 24 hr included in the NMA. There were 28 studies with low ROB, 29 with high ROB, and 13 with some concerns of bias. Judgments regarding each ROB for independent study item are presented as percentages across all the included trials in Fig. 4. Risk of bias for secondary outcomes is discussed in subsequent sections.

TABLE 1 Postoperative sore throat at 24 hr

Benzydamine	7.55 (3.36 to 17.97)	1.13 (0.36 to 3.53)	2.99 (0.67 to 13.14)	1.19 (0.30 to 5.01)	4.95 (1.08 to 24.44)	1.60 (0.62 to 4.37)	5.14 (2.06 to 13.37)	1.06 (0.21 to 5.26)	0.75 (0.20 to 2.71)	0.86 (0.32 to 2.44)
Intracuff air		0.15 (0.07 to 0.32)	0.40 (0.12 to 1.32)	0.16 (0.05 to 0.51)	0.65 (0.16 to 2.53)	0.21 (0.12 to 0.37)	0.68 (0.38 to 1.20)	0.14 (0.03 to 0.55)	0.10 (0.03 to 0.26)	0.11(0.06 to 0.22)
		Intracuff lidocaine	2.67 (0.90 to 7.93)	1.06 (0.26 to 4.38)	4.37 (0.95 to 21.15)	1.43 (0.54 to 3.70)	4.56 (1.85 to 11.65)	0.93 (0.18 to 4.63)	0.67 (0.18 to 2.41)	0.77 (0.29 to 2.09)
		Intracuff 0.9% saline		0.40 (0.07 to 2.12)	1.67 (0.27 to 10.05)	0.54 (0.14 to 2.04)	1.74 (0.45 to 6.37)	0.35 (0.05 to 2.33)	0.25 (0.05 to 1.18)	0.29 (0.07 to 1.07)
		Inhaled corticosteroids			4.15 (0.71 to 23.99)	1.35 (0.37 to 4.64)	4.34 (1.20 to 15.40)	0.89 (0.14 to 5.46)	0.62 (0.13 to 2.89)	0.72 (0.19 to 2.74)
		Water- based lubricant				0.33 (0.07 to 1.39)	1.03 (0.28 to 3.92)	0.21 (0.03 to 1.41)	0.15 (0.03 to 0.86)	0.17 (0.05 to 0.66)
		Ketamine				3.20 (1.48 to 7.12)	0.66 (0.14 to 2.97)		0.47 (0.15 to 1.36)	0.54 (0.23 to 1.28)
		Lidocaine						0.20 (0.04 to 0.93)	0.15 (0.04 to 0.46)	0.17 (0.08 to 0.33)
		Liquorice							0.71 (0.12 to 4.11)	0.82 (0.18 to 3.84)
		Magnesium								1.15 (0.36 to 3.90)
		Corticosteroids								

Quantities reported are odds ratios with 95% credible intervals combining direct/indirect estimates. Both point estimates and credible intervals are considered when ranking treatments

Publication bias

We constructed a funnel plot for pairwise comparisons (using R software) to visually inspect publication bias. Most trials were symmetrically distributed and no obvious publication bias was noted (Fig. 5).

Inconsistency

To estimate/locate network inconsistency, we used net-heat plot and node-splitting analysis. Net-heat (eFig. 2; ESM) helped us estimate contribution of a direct comparison in the overall pairwise comparison result (that includes both indirect and direct estimate). It also helped us to estimate

the inconsistency contributed by individual comparison to the overall network. The node split model compared pairwise direct, indirect, and network estimates for all the treatments. For all comparisons, both direct and indirect values corroborated well. No *P* values evaluating differences between direct and indirect estimates were statistically significant (Fig. 6).

Our results showed that, after combining the evidence from direct and indirect estimates, magnesium was the best prophylactic agent for prevention of postoperative sore throat at 24 hr and had a 36% probability of being the best treatment. There were negligible (0%) chances of magnesium being the worst agent. Liquorice ranked second with a 19.2% probability of being the best, and

Fig. 3 Risk of bias summary for postoperative sore throat at 24 hr.

Fig. 4 Risk of bias bar chart for postoperative sore throat at 24 hr. The colours in the bars next to each row/criterion represent percentage of total studies falling within the high/low/some concerns category.

Fig. 5 Comparison-adjusted funnel plots of publication bias for postoperative sore throat at 24 hr. Benz = benzydamine; IcAr = intracuff air; IcLi = intracuff lidocaine; IcNS = intracuff normal saline; IhSt = inhaled steroid; Keta = ketamine; KYJe = water-based lubricant; Lido = lidocaine; Liqr = liquorice; Mg = magnesium; Ster = corticosteroid.

corticosteroids ranked third with a 14.4% probability of being the best prophylactic agent for postoperative sore throat at 24 hr. Lidocaine was the least effective agent with a 52% probability of being the worst treatment. Certainty

of evidence was low because of inconsistency, imprecision, and indirectness among the included trials (Table 2).

Fig. 6 Forest plot showing direct, indirect, and network estimates of effect for pairwise comparisons of interventions for postoperative sore throat at 24 hr. Benz = benzydamine; IcAr = intracuff air; IcLi = intracuff lidocaine; IcNS = intracuff normal saline; IhSt = inhaled steroid; Keta = ketamine; KYJe = water-based lubricant; Lido = lidocaine; Mg = magnesium; Ster = corticosteroid.

Fig. 6 continued

Sore throat at 4–6 hr

We were able to include eight treatment nodes (42 trials) in our network for this parameter and included a total of 4,813 patients (eFig. 3; ESM). The comparative absolute OR values for early sore throat are shown in Table 3. Inhaled corticosteroids (OR, 0.03; 95% CrI, 0.00 to 0.33) appeared to be associated with lowest early sore throat with a 92.13% probability of being the best treatment. A random-effects model was used for this parameter with a DIC of 172.22 (with 91 data points and a residual deviance of 93.7). The rank order of preference for grading all the included treatments and estimated network inconsistency based upon the net-heat plot are shown in eFigs 4 and 5 (ESM), respectively. Risk of bias across the studies is reported in eFig. 6 (ESM).

Cough at 24 hr

The network for cough at 24 hr included ten treatment nodes (23 trials) with a total of 2,405 patients (eFig. 7; ESM). The comparative OR of cough for all treatment groups is shown in Table 4. Liquorice (OR, 0.00; 95% CrI, 0.00 to 0.28) was associated with the lowest occurrence of cough at 24 hr (60.77% probability of being the best treatment). The combined probability of liquorice and benzydamine for being the best treatment associated with lowest incidence of cough was 99.66%. The DIC for the random-effects modelling for this parameter was 98.13 (with 57 data points and residual deviance of 52.9). The rank order of preference for grading all the included treatments for this parameter is shown in eFig. 8 (ESM). Model inconsistency was evaluated using the net-heat plot shown in eFig. 9 (ESM). Risk of bias across the studies is presented in eFig. 10 (ESM).

Hoarseness at 24 hr

We were able to construct a network for this outcome with ten treatment nodes (24 trials) and a total of 2,600 patients (eFig. 11; ESM). The OR for hoarseness after each treatment is shown in Table 5. Use of magnesium (OR, 0.00; 95% CrI, 0.00 to > 100) was associated with the lowest hoarseness and had a 73.63% probability of being the best agent. Results are reported based on the random-effects model with a DIC of 97.59 (with 58 data points and a residual deviance of 53.8). The relative grading of treatments in terms of treatment efficacy is shown in eFig. 12 (ESM). We evaluated the network inconsistency using the net-heat plot as shown in eFig. 13 (ESM), and ROB across the studies is presented in eFig. 14 (ESM).

Quality of evidence and recommendations

We prepared a summary of finding (SoF) table based on GRADE Pro recommendations comparing all the active treatments with the control (intracuff air) for all the outcomes. The evidence shows that use of any active agent was beneficial compared with the control, but the quality of this was low for the primary and secondary outcomes (Table 6). The direct estimate was assessed using the ROB, inconsistency, and publication bias. The final pooled mixed estimate was assessed using the rating of the direct estimate (if high and dominant in contribution) followed by assessment for incoherence and imprecision.

Discussion

Our NMA provides a comprehensive synthesis of evidence for topical prophylactic treatment of sore throat in adult

TABLE 2 Postoperative sore throat at 24 hr network meta-analysis summary of finding table

Patients: Adult (18-75 years) undergoing surgery with endotracheal tube Intervention: Multiple topical agents Comparator (Reference): Intracuff air Outcome: sore throat Timing: 24 hours Setting: Postoperative period						
Total studies (Total population):	Anticipated absolute effect (95% CrI)			Relative effect (95% CrI) Network estimate	Certainty of evidence	Probability
	Without intervention	With intervention	Odds Ratio			Best Treatment Worst Treatment
Magnesium (6 RCTs; 511 participants)	221/1000	45/1000	0.17 (0.09 to 0.32)	0.10 (0.03 to 0.26)	⊕⊕ LOW†	0.36 0.00
Liquorice (3 RCTs; 197 participants)	724/1000	353/1000	0.21 (0.11 to 0.38)	0.14 (0.03 to 0.55)	⊕⊕ LOW†‡	0.192 0.003
Corticosteroids (12 RCTs; 1086 participants)	651/1000	178/1000	0.12 (0.09 to 0.15)	0.11 (0.06 to 0.22)	⊕⊕ LOW†#	0.144 0.00
Benzydamine (9 RCTs; 1192 participants)	255/1000	72/1000	0.23 (0.16 to 0.32)	0.13 (0.30 to 0.06)	⊕⊕ LOW†	0.12 0.000
Inhaled corticosteroids (4 RCTs; 266 participants)	436/1000	127/1000	0.19 (0.10 to 0.35)	0.16 (0.05 to 0.51)	⊕⊕ LOW‡	0.112 0.001
Intracuff lidocaine (7 RCTs; 691 participants)	534/1000	181/1000	0.19 (0.13 to 0.27)	0.15 (0.07 to 0.32)	⊕⊕ LOW†‡	0.065 0.000
Intracuff 0.9% Saline (2 RCTs; 155 participants)	610/1000	483/1000	0.60 (0.31 to 1.15)	0.40 (0.12 to 1.32)	⊕⊕ LOW†‡	0.004 0.046
Ketamine (17 RCTs; 1377 participants)	364/1000	137/1000	0.28 (0.21 to 0.36)	0.21 (0.12 to 0.37)	⊕⊕ LOW†‡	0.002 0.000
Water soluble jelly (No direct evidence, indirect evidence only)	No trials	No trials	Not estimable	0.65 (0.16 to 2.53)	⊕⊕ LOW†#	0.001 0.256
Lidocaine (14 RCTs; 1350 participants)	379/1000	313/1000	0.75 (0.60 to 0.94)	0.68 (0.38 to 1.20)	⊕⊕ LOW†‡	0.000 0.052
Intracuff air	No estimable	No estimable	No estimable	Reference comparator	Reference comparator	0.000 0.642
Rows represent direct comparisons ***Estimates are reported as odds ratio. CrI: credible interval. †Inconsistency ‡Imprecision #Indirectness

TABLE 3 Postoperative sore throat at 4–6 hr

Benzylamine	5.00 (2.38 to 10.53)	0.12 (0.01 to 1.87)	11.69 (1.32 to 110.41)	1.22 (0.50 to 2.95)	5.02 (2.11 to 11.82)	1.29 (0.42 to 4.23)	1.72 (0.65 to 4.54)
Intracuff air		0.03 (0.00 to 0.33)	2.38 (0.28 to 20.44)	0.24 (0.14 to 0.43)	1.01 (0.50 to 1.97)	0.26 (0.11 to 0.65)	0.35 (0.17 to 0.70)
Inhaled corticosteroids			94.05 (3.66 to 147.93)	9.89 (0.71 to 158.08)	40.19 (2.79 to 711.38)	10.38 (0.67 to 201.36)	13.70 (0.96 to 237.51)
Water-based lubricant				0.10 (0.01 to 0.90)	0.43 (0.05 to 3.46)	0.11 (0.01 to 1.13)	0.15 (0.02 to 1.18)
Ketamine					4.11 (1.71 to 9.89)	1.05 (0.41 to 2.81)	1.41 (0.56 to 3.35)
Lidocaine						0.26 (0.09 to 0.80)	0.34 (0.15 to 0.76)
Magnesium							1.33 (0.42 to 4.09)
Corticosteroids							

Quantities reported are 95% credible intervals of the final odds ratios combining direct/indirect estimates. Both point estimates and credible intervals are considered when ranking treatments.

patients undergoing surgery with an ETT. Our results revealed that magnesium, liquorice, and corticosteroid were the three topical agents most associated with a decreased postoperative sore throat.

Efficacy of preoperative topical administration of magnesium sulfate in preventing sore throat in adult patients was recently examined in two meta-analyses.^{85,86} Singh *et al.*⁸⁵ have reported that the number needed to treat was around five indicating a large prophylactic effect. No statistical heterogeneity was found for incidence of sore throat by both authors. We identified few direct comparisons of topical magnesium and other active treatments; however, our network analysis provided indirect evidence of superior efficacy of topical magnesium. The clinical utility of topical magnesium is limited by the absence of a commercially available preparation in North America and the United Kingdom and by the limited knowledge of its utility among healthcare professionals.

Topical lidocaine, applied as a jelly or spray, was associated with a high probability of being the worst outcome. Lidocaine jelly used in various trials contained additives like chlorhexidine gluconate, methyl hydroxybenzoate, and propyl hydroxybenzoate for antiseptic effect.^{87,88} These additives can cause hypersensitivity reactions or induce allergic dermatitis. Further, they may form dry sediments in the trachea, which irritate the airway and increase sore throat. Similarly various additives or the alkalized solvents added to lidocaine spray might have added to the damage inflicted on the tracheal mucosa during intubation, thus negating the membrane stabilizing effect of lidocaine, resulting in

increased incidence of sore throat.⁸⁹ Though an initial meta-analysis¹⁰ reported efficacy of topical lidocaine in reducing sore throat, a recent update by Liao *et al.*⁹⁰ found that lidocaine lubricants in jelly, ointment, or spray, if not harmful, were not effective in preventing postoperative sore throat.

On the other hand, when administered as a cuff inflation medium, lidocaine ranked above lidocaine jelly and spray. Cuff inflation exerts a continuous topical anesthetic effect. Also, unlike air, intracuff lidocaine was not associated with an increase in the cuff pressure due to diffusion of nitrous oxide.⁹¹ Further, absence of any additives in intracuff lidocaine solution prevents further damage.

Our analysis has a number of limitations. Unlike a conventional meta-analysis, networks rely heavily on making indirect estimates, so credibility intervals often overlap. As a result, networks give probability of a rank order rather than an absolute rank order. Thus, readers must exercise caution when interpreting these findings. Further, it is often not possible to define “prior distributions” in Bayesian NMA, and calculations are needed to derive large standard deviation values from the available data. This may compromise precision of results. Also, most Bayesian NMA software does not allow for robust exploration of network inconsistency. We attempted to overcome this limitation with the use of a net-heat plot (frequentist approach) and node split model (Bayesian approach). Further, based on fitting of a logistic regression model using an MCMC algorithm, one can obtain estimates of the posterior distributions of not only the regression coefficients (β) but also any function of the regression

TABLE 4 Cough at 24 hr

Benzydamine	> 100 (8.01 to > 100)	>100 (1.47 to > 100)	> 100 (1.32 to > 100)	> 100 (15.72 to > 100)	> 100 (2.01 to > 100)	> 100 (6.59 to > 100)	0.00 (0.00 to > 100)	> 100 (0.39 to > 100)	> 100 (2.42 to > 100)
Intracuff air		0.24 (0.03 to 1.72)	0.20 (0.03 to 1.40)	2.08 (0.41 to 10.15)	0.31 (0.06 to 1.74)	0.83 (0.32 to 2.10)	0.00 (0.00 to 0.28)	0.07 (0.01 to 0.84)	0.30 (0.14 to 0.66)
		Intracuff lidocaine	0.80 (0.05 to 12.95)	8.75 (0.71 to 117.84)	1.31 (0.09 to 18.30)	3.45 (0.39 to 33.03)	0.00 (0.00 to 1.31)	0.28 (0.01 to 7.38)	1.27 (0.14 to 11.03)
		Inhaled corticosteroids		10.93 (0.84 to 145.75)	1.63 (0.11 to 25.48)	4.26 (0.48 to 40.65)	0.00 (0.00 to 1.48)	0.35 (0.01 to 9.25)	1.56 (0.19 to 13.60)
		Water-based lubricant			0.15 (0.02 to 1.5)	0.40 (0.09 to 1.85)	0.00 (0.00 to 0.13)	0.03 (0.00 to 0.68)	0.15 (0.03 to 0.65)
					Ketamine	2.64 (0.37 to 17.93)	0.00 (0.00 to 0.82)	0.21 (0.01 to 4.22)	0.96 (0.16 to 5.90)
					Lidocaine		0.00 (0.00 to 0.32)	0.08 (0.01 to 1.20)	0.37 (0.14 to 0.94)
					Liquorice			>100 (0.19 to >100)	>100 (1.05 to >100)
								Magnesium	4.61 (0.31 to 66.63)
									Corticosteroids

Quantities reported are 95% credible intervals of the final odds ratios combining direct/indirect estimates. Both point estimates and credible intervals are considered when ranking treatments.

TABLE 5 Hoarseness at 24 hr

Benzydamine	8.74 (1.35 to 84.42)	1.59 (0.09 to 35.99)	1.78 (0.07 to 65.85)	2.12 (0.16 to 33.83)	8.73 (0.87 to 125.42)	2.51 (0.31 to 32.73)	6.07 (0.86 to 68.74)	0.00 (0.00 to > 100)	2.95 (0.41 to 31.29)
Intracuff air		0.18 (0.02 to 1.52)	0.20 (0.01 to 3.06)	0.24 (0.04 to 1.22)	1.02 (0.24 to 3.81)	0.28 (0.10 to 0.80)	0.70 (0.32 to 1.478)	0.00 (0.00 to >100)	0.34 (0.16 to 0.66)
		Intracuff lidocaine	1.11 (0.22 to 5.86)	1.32 (0.08 to 19.57)	5.64 (0.40 to 69.10)	1.57 (0.15 to 17.15)	3.84 (0.38 to 38.92)	0.00 (0.00 to >100)	1.88 (0.19 to 18.30)
		Intracuff 0.9% saline		1.20 (0.04 to 27.43)	5.10 (0.23 to 102.78)	1.44 (0.08 to 6.16)	3.52 (0.20 to 59.46)	0.00 (0.00 to >100)	1.72 (0.09 to 26.82)
				Inhaled corticosteroids	4.31 (0.51 to 41.03)	1.19 (0.17 to 10.06)	2.96 (0.48 to 21.31)	0.00 (0.00 to >100)	1.41 (0.23 to 9.72)
				Water-based lubricant		0.28 (0.05 to 1.58)	0.69 (0.19 to 2.63)	0.00 (0.00 to >100)	0.33 (0.10 to 1.18)
						Ketamine	2.47 (0.69 to 8.71)	0.00 (0.00 to >100)	1.19 (0.34 to 3.79)
						Lidocaine		0.00 (0.00 to >100)	0.48 (0.21 to 1.06)
								Magnesium	>100 (0.00 to >100)
									Corticosteroids

Quantities reported are 95% credible intervals of the final odds ratios combining direct/indirect estimates. Because of few or zero events in one of the comparative groups, the relative odds ratio for some variables are extremely large, these resulting odds ratio values have been represented as values > 100 in the above table. Both point estimates and credible intervals are considered when ranking treatments.

coefficients (e.g., the OR exp [β]). Posterior means and 95% CrI can be used to summarize these posteriors.⁹²

We found that covariates of interest did not have uniform distribution across all the treatment groups. This

was because there were fewer comparisons of liquorice, water-based lubricant and inhaled corticosteroids than of lidocaine, ketamine, and benzydamine. This is likely to have an impact on the ability to accurately estimate

TABLE 6 Summary of findings for all topical agents compared with control for different outcomes (based on GRADEPro)

Patient or population: Adult (18–75 yr) undergoing surgery with endotracheal tube Intervention: Multiple topical agents Comparison: Intracuff air Outcomes: Various outcomes Timing: 24 hours Setting: Postoperative period						
Outcomes	Anticipated absolute effects* (95% CrI)		Relative effect (95% CrI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with topical agents				
Postoperative sore throat at 24 hr	390 per 1,000 (360.2 to 420.6)	201 per 1,000 (177.3 to 227.0)	0.52 (0.45 to 0.60)	7,141 (70 RCTs)	⊕⊕○○ LOW†‡	For combined direct and indirect evidence, magnesium (OR, 0.10; 95% CrI, 0.03 to 0.26) followed by steroid (OR, 0.11; 95% CrI, 0.06 to 0.22) and liquorice are the best prophylactic agents.
Postoperative sore throat at 4–6 hr	444 per 1,000 (413.5 to 475.0)	261 per 1,000 (234.7 to 289.1)	0.59 (0.52 to 0.67)	4,813 (42 RCTs)	⊕⊕○○ LOW#	For combined direct and indirect evidence, inhaled corticosteroids (OR, 0.03; 95% CrI, 0.00 to 0.33) followed by benzydamine (OR, 5.00; 95% CrI, 2.38 to 10.53) and ketamine are the best prophylactic agents.
Cough at 24 hr	284 per 1,000 (256.9 to 312.7)	130 per 1,000 (110.6 to 152.3)	0.46 (0.38 to 0.55)	2,405 (23 RCTs)	⊕⊕○○ LOW†‡	For combined direct and indirect evidence, benzydamine (OR, > 100; 95% CrI, 8.01 to >100) followed by liquorice (OR, 0.00; 95% CrI, 0.00 to 0.28) and magnesium are the best prophylactic agents.
Hoarseness at 24 hr	281 per 1,000 (254.0 to 309.7)	184 per 1,000 (161.2 to 209.2)	0.65 (0.56 to 0.77)	2,600 (24 RCTs)	⊕⊕○○ LOW†‡	For combined direct and indirect evidence, magnesium (OR, 0.00; 95% CrI, 0.00 to > 100) followed by benzydamine (OR, 8.74; 95% CrI, 1.35 to 84.42) and intracuff lidocaine are the best prophylactic agents.

*The risk in the intervention group (and its 95% CrI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CrI)

[†]Inconsistency; [‡]Imprecision; [#]Indirectness. CrI = credible interval; OR = odds ratio; RCT = randomized-controlled trial; relative effect presented as odds ratios with CrI

GRADE working group of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

contribution of covariates to the observed outcomes. Further, given the number of interventions available with huge variations, we had to group various topical medication routes together for comprehensibility. We acknowledge that there is a possibility that variations in drug delivery methods within topical groups could have affected the outcome, but there was no feasible way of performing a separate subgroup analysis given the small number of patients in each subgroup. We also planned to perform meta-regression for nature and duration of surgery. Nevertheless because of marked variations among these variables, a valid subgrouping was not deemed appropriate.

Given that it is difficult to separate the top three agents in this regard, other factors such as local availability and ease of administration may determine the most appropriate choice in different settings. Estimation of appropriate doses was not possible because of varying doses used in enrolled trials. Similarly, in absence of reporting of adverse effect in various studies, we could not conclude which drug was associated with least adverse effects.

In conclusion, topical magnesium showed the greatest probability of reducing postoperative sore throat at 24 hr (low quality of evidence) following surgery. This was followed by liquorice and corticosteroid (low quality of evidence) application. Intracuff air and topical lidocaine were associated with the lowest probability of a good outcome. Inhaled corticosteroids were found to be the most effective modality in decreasing early (4–6 hr) sore throat. Benzydamine and liquorice ranked as top agents for prevention of cough at 24 hr while magnesium and benzydamine scored highly for prevention of hoarseness at 24 hr. More evidence is needed to formulate stronger recommendations in favour of efficacy of magnesium to prevent sore throat.

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