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Comparative Efficacy of 6 Topical Pharmacological Agents for Preventive Interventions of Postoperative Sore Throat After Tracheal Intubation: A Systematic Review and Network Meta-analysis

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BACKGROUND: Topical pharmacological agents typically used to treat postoperative sore throat (POST) after tracheal intubation include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, lidocaine, *Glycyrrhiza* (licorice), and *N*-methyl-D-aspartate (NMDA) receptor antagonists (including ketamine and magnesium). However, the optimal prophylactic drug remains elusive.
METHODS: The literature published before September 8, 2019 was searched on the PubMed, the Embase, the Web of Science, and the Cochrane Library. Randomized controlled trials (RCTs) covering topical prophylactic medications for patients with POST were included. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to assess the quality of evidence. The primary outcome is the risk of POST. Combining both direct and indirect evidence, a network meta-analysis was performed to assess odds ratios (ORs) between the topical pharmacological agents and surface under the cumulative ranking (SUCRA) curve for the treatment-based outcomes. This study is registered with PROSPERO, number CRD42020158985.
RESULTS: Sixty-two RCTs (at least 73% of which were double blinded) that included a total of 6708 subjects and compared 6 categories of drugs and/or placebos were ultimately enrolled. All preventive interventions except lidocaine were more effective than placebo at the 4 time intervals. Lidocaine (OR: 0.35, 95% credible interval [CrI], 0.16-0.79) has a greater POST preventative intervention effect than the placebo at a time interval of only 2 to 3 hours after surgery. Relative to lidocaine, the risk of POST except 2 to 3 hours was lower for the following treatments: corticosteroids, ketamine, magnesium, NSAIDs, and *Glycyrrhiza*. The NMDA receptor antagonists studied here included ketamine and magnesium. Magnesium generally demonstrated greater benefit than ketamine at 24 hours postsurgery/extubation (OR: 0.41, 95% CrI, 0.18-0.92). Compared with ketamine, corticosteroids were associated with a reduced risk of POST during the 4 to 6 hours (OR: 0.40, 95% CrI, 0.19-0.83) and 24 hours (OR: 0.34, 95% CrI, 0.16-0.72) time intervals. During the 2 to 3 hours time interval, *Glycyrrhiza* (OR: 0.38, 95% CrI, 0.15-0.97) was more efficacious than magnesium.
CONCLUSIONS: Our analysis shows that, among the 6 topical medications studied, lidocaine is not optimal for topical use to prevent POST. Glycyrrhizin, corticosteroids, NSAIDs, and NMDA receptor antagonists (ketamine and magnesium) are associated with a reduced postoperative pharyngeal pain across the 4 postsurgical time intervals studied, all of which can be chosen according to the clinical experience of the anesthesiologists and the patient preferences and are recommended for the reduction of postoperative throat pain. (Anesth Analg 2021;133:58–67)

KEY POINTS

- **Question:** Are there optimal prophylactic agents among topical medications that prevent postoperative sore throat (POST)?
- **Findings:** Glycyrrhizin, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and *N*-methyl-D-aspartate (NMDA) receptor antagonists (ketamine and magnesium) are associated with a reduced postoperative pharyngeal pain across the 4 postsurgical time intervals studied; lidocaine is not optimal for topical use to prevent POST.
- **Meaning:** Glycyrrhizin, corticosteroids, NSAIDs, and NMDA receptor antagonists (ketamine and magnesium) can be chosen according to the clinical experience of anesthesiologists and patient preferences and are recommended for the reduction of postoperative throat pain.

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GLOSSARY

ASA = American Society of Anesthesiologists; **CI** = confidence interval; **CrI** = credible interval; **ETT** = endotracheal tube; **GRADE** = Grading of Recommendations Assessment, Development, and Evaluation; **NMDA** = *N*-methyl-D-aspartate; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **ORs** = odds ratios; **POST** = postoperative sore throat; **PRISMA** = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **PSRF** = potential scale reduction factor; **RCTs** = randomized controlled trials; **ROB** = risk of bias; **RR** = relative ratio; **SUCRA** = surface under the cumulative ranking

Postoperative sore throat (POST) is a common consequence of general anesthesia with endotracheal intubation, with an estimated risk ranged from 14.4% to 62%.[1,2] It ranks as the eighth most undesirable clinical anesthesia outcome and negatively affects patient satisfaction and the quality of care.[3] Mucosal injury, inflammation, and erosion caused by the endotracheal intubation are all possible contributors to POST occurrence.[4–8] Thus, effective prevention and improvement in care for POST are needed.

Systematic reviews show that steroids, lidocaine, nonsteroidal anti-inflammatory drugs (NSAIDs), *N*-methyl-D-aspartate (NMDA) receptor antagonists, and *Glycyrrhiza* (licorice) are used topically—each with different mechanisms of action and varying degrees of success for POST prevention.[9–17] Studies suggest that NSAIDs have anti-inflammatory, analgesic, and antipyretic mechanisms of action. In addition, corticosteroids prevent postoperative complications via anti-inflammatory mechanisms. The NMDA receptor antagonists (magnesium and ketamine) utilize antinociceptive and anti-inflammatory pathways that relieve POST. Ingredients in licorice reportedly have antitussive and anti-inflammatory effects. One meta-analysis found that lidocaine lubricants applied to the tips of the endotracheal tube (ETT) were not effective.[18] However, differences in clinical use—including variation in doses and administration routes—mean that conclusions on the use of lidocaine for POST prevention are equivocal. A consensus on the optimal prophylactic agents for the POST treatment remains controversial. A large clinical trial comparing the treatment options is needed to answer this question.

To this end, we compiled data from all systematic reviews and randomized controlled trials (RCTs) that compared the major prophylactic topical drugs across the 4 time intervals and performed a meta-analysis to evaluate the risk of POST following the surgery/extubation.

METHODS

Search Strategy

A systematic review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplemental Digital Content, Appendix 1, http://links.lww.com/AA/D435). Our protocol was registered at PROSPERO (CRD42020158985). Four electronic databases (ie, the PubMed, the Embase, the Web of Science, and the Cochrane Library) were used to search without language restrictions from the date of inception. We used the following search terms: "intubation, intratracheal" OR "endotracheal intubation" "pharyngitis" OR "pharyngit*" OR "(sore* OR inflamm* OR infect*) NEAR/5 throat" OR "(endotracheal OR intratracheal) NEAR/5 intub*" in combination with a list of all included topical application drugs for POST (Supplemental Digital Content, Appendix 2, http://links.lww.com/AA/D435). We searched clinical trial registries for unpublished trials and the reference lists of previous meta-analyses to identify additional studies. The search was last conducted on December 17, 2019.

Selection Criteria

Trials were included in this meta-analysis if they met the following criteria: (1) research type: RCTs; (2) research subjects: trials were randomized design with subjects >18 years; (3) interventions: topical pharmacological agents for the preventive interventions of POST, commonly used doses of the 6 interventions are listed (Supplemental Digital Content, Appendix 4, http://links.lww.com/AA/D435); and (4) outcomes included the risk of POST 24 hours after surgery/extubation. Exclusion criteria included (1) emergency operation, (2) alkalinized lidocaine solution filled the tracheal tube cuff, (3) duplicate publications, and (4) appropriate data could not be extracted or calculated from the published results.

Data Extraction

The full manuscripts of publications meeting the inclusion criteria were reviewed independently by 2 investigators (G.W. and Y.Q.), and the relevant data were extracted into an electronic database, including trial information (ie, author, publication year, sample size, types of intervention, and control), population characteristics (ie, sex, age, and American Society of Anesthesiologists [ASA] physical status), study characteristics (ie, country, ETT size, and surgery type), study intervention, that is, drug administration data (ie, dosage, time, and mode of application), reported outcomes (including

POST risk after surgery/extubation at the following time intervals: 0–1, 2–3, 4–6, and 24 hours), and information on methodology. Disagreements between the 2 reviewers were resolved by consensus and, if necessary, by consultation with a third reviewer (L.W.).

Quality Assessment

The Cochrane risk of bias (ROB) tool was used by 2 reviewers to independently assess the quality of the included studies. The ROB tool includes randomization, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. In addition, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was used to assess the quality of evidence contributing to each network estimate, which characterizes the quality of the evidence on the basis of the study limitations, imprecision, inconsistency, indirectness, and publication bias for the primary outcomes.[19]

Outcomes

The risk of POST after surgery/extubation was the primary outcome of this study. As there is no established definition of POST, the definition used by each study was accepted. Most studies utilized a 4-level classification system (ie, none, mild, moderate, or severe) and a 4-point scale (0–3) for postoperative soreness to categorize the presence and the severity of POST. The sum of severe, moderate, and mild cases was used to calculate the risk of POST. As different time intervals were used for the POST assessment, we recategorized the outcomes into 4 subgroups: 0 to 1, 2 to 3, 4 to 6, and 24 hours.

Data Analysis

Standard pairwise meta-analyses were performed using the DerSimonian–Laird random effects model to directly compare different treatment arms. The point estimates of odds ratios (ORs) and 95% confidence intervals (CIs) of direct comparisons between the 2 treatments were calculated to measure the effect. The I^2 statistic was used to calculate the heterogeneity, with the following definitions: I^2 values <30% were considered meaningless. Heterogeneity P values <.05 were considered significant.

In addition to the direct comparison of the studies for meta-analyses, a multiple treatment meta-analysis with a random-effects model within a Bayesian framework in ADDIS 1.16.8 (Drug Information Systems, Groningen, the Netherlands) was conducted. The prior evaluation and data were processed by using the Markov chain Monte Carlo algorithms. Noninformative uniform and normal previous distributions were chosen. Previous distributions were assigned for both the OR effect size and the between-study variance. Parameters for the ADDIS software were as follows: number of chains, 4; tuning iterations, 20,000; simulation iterations, 100,000; thinning interval, 10; inference samples, 20,000; and variance scaling factor, 2.5. The effect and posterior distributions of model parameters were generated.[20,21] By using this method, both direct and indirect evidence of treatment pairs in a single joint analysis were combined.[22,23] The network framework enabled both analyses of the direct within-trial comparisons of the 2 treatments and the incorporation of indirect comparisons built from the 2 trials having a treatment in common.

The treatment hierarchy was summarized and presented as the surface under the cumulative ranking (SUCRA) curve and mean ranks. Therapy is considered to be optimal at a SUCRA value of 100% and the least effective at 0%. The sum of probabilities for the interventions at each rank is 100%, and the sum of probabilities across ranks is 100% for each intervention.

The consistency hypothesis of the whole analytical network was assessed. A loop-specific method was used to determine the local inconsistency of each closed loop. After that, the node-splitting method was used to assess model inconsistency by separating evidence into indirect and direct categories and then calculating its P value. If the P value of the node-splitting analysis is <.05, a nonconsistency model would be used. Otherwise, the consistency model would be used. The convergence of the model was determined by the potential scale reduction factor (PSRF) of the Brooks–Gelman–Rubin method. PSRF closer to 1 indicated the better convergence; generally, PSRF <1.2 was acceptable. To assess the degree of uncertainty in the locally estimated effect size, the prediction interval plots were applied to integrate the degree of heterogeneity.[24] Uncertainty affected by heterogeneity was defined as disagreement between the CIs of relative treatment effects and their predictive intervals. The transitivity assumption underlying network meta-analysis was evaluated by comparing the distribution of clinical variables, which could act as effect modifiers across treatment comparisons. The SPSS statistics 26.0 (IBM Corporation, Armonk, NY) was used to show a box plot of mean study of the ages for each of the 6 interventions.

The contribution of each direct comparison to the estimated overall effect of each network meta-analysis was estimated using contribution plots as these are beneficial for the assessment of overall quality of the data in the network meta-analysis.[24] Comparison-adjusted funnel plots were used to analyze the publication bias.

RESULTS

Study Characteristics

The titles and abstracts of a total of 6708 studies were identified for review (Figure 1). Full texts of potentially eligible articles published from 1997 to 2019 were retrieved for further assessment after the initial screening. A final total of 6473 studies were excluded, and 62 studies were found eligible for the meta-analysis. The eligible studies included 4343 subjects who received 1 of the 6 treatments. The evidence network of the controlled trials that reported treatment outcomes at each of the 4 time intervals for NSAIDs, corticosteroids, lidocaine, *Glycyrrhiza*, ketamine, magnesium, and placebo is shown. For all the included studies reporting on the 0 to 1 hour interval, 72.54% (37 of 51) were 2-arm studies and 27.46% (14 of 51) were multiple-arm studies. For the 2 to 3 hours interval, 79.16% (19 of 24) were 2-arm studies and 20.84% (5 of 24) were multiple-arm studies. For the 4 to 6 hours interval, 68% (34 of 50) were 2-arm studies and 32% (16 of 50) were multiple-arm studies. At the 24 hours postsurgical interval, 71.67% (43 of 60) were 2-arm studies and 28.33% (17 of 60) were multiple-arm studies (Figure 2). Fifty-five trials (88.7%) were placebo controlled. A total of 1091 (25.12%) subjects were assigned to NSAIDs treatment, 903 (20.79%) to corticosteroids treatment, 978 (22.51%) to lidocaine treatment, 324 (7.47%) to *Glycyrrhiza* treatment, 604 (13.9%) to ketamine treatment, and 443 (10.21%) to magnesium treatment. Patient ages ranged from 18 to 70 years with a mean age of 42.8 years. In total, across the different studies, 16 different comparisons were reported and were designed to assess the primary outcome of the present study. We investigated the following 1 time intervals for the reported risk of POST: 0 to 1, 2 to 3, 4 to 6, and 24 hours. In total, 51 studies (1–8, 10, 12, 15, 17–29, 31–41, 43–44, 46–54, 56, 58–60, and 62) reported adverse event data for the 0 to 1 hour postsurgical interval; 24 studies (1, 3–4, 10–12, 14–15, 24–25, 29, 33, 35–36, 39–41, 44–45, 47, and 51–54) reported data for the 2 to 3 hours postsurgical period; 50 studies (1–15, 18–19, 21–25, 28–31, 33–36, 39–48, 50–56, 58, and 60–61) reported data for the 4 to 6 hours postsurgical interval; and 60 studies (1–11, 13–29, and 31–62) reported data for the 24 hours postsurgery. The characteristics of the 62 included studies are summarized in Supplemental Digital Content, Appendix 4, http://links.lww.com/AA/D435.

Supplemental Digital Content, Appendix 5, http://links.lww.com/AA/D435, lists our assessment of the methodological quality of the 62 included studies, which utilized the Cochrane bias risk tool assessment. Blinding was mentioned in all included studies. Twenty-two studies detailed the methods on allocation concealment, 12 of which were coded utilizing a computer-generated table of randomized numbers (5, 12, 15, 18–19, 22, 25, 31, 42, 53–54, and 56). Ten studies used light-tight envelopes (9, 17, 20, 23, 26–27, 32–35, 39, and 47). Of all included studies, 71.4% of studies blinded both participants and investigators (1–4, 8, 11–12, 15–28, 30, 32–35, 37–40, 44–52, 55–57, and 60–61), 12.7% blinded participants only (5, 10, 13, 31, 36, and 41–43), and 15.8% proposed study blinding but did not specify the blinded population (6, 7, 9, 14, 29, 53–54, 58–59, and 62). Drug administration data (dosage and time and mode of application) were provided (Supplemental Digital Content, Appendix 4, http://links.lww.com/AA/D435).

Results From the Network Meta-analysis of the Outcomes

All the preventive interventions except lidocaine were more effective than the placebo at the 4 time intervals. Lidocaine (OR: 0.35, 95% credible interval [CrI], 0.16-0.79) had a greater POST preventive intervention effect than the placebo at a time interval of only 2 to 3 hours after surgery. Relative to lidocaine, except for the 2 to 3 hours time interval, the risk of POST was lower for the following treatments: corticosteroids, ketamine, magnesium, NSAIDs, and *Glycyrrhiza*.

The NMDA receptor antagonists studied here included ketamine and magnesium. Magnesium showed overall greater benefit than ketamine at 24 hours after surgery/extubation (OR: 0.41, 95% CrI, 0.18-0.92). Compared with ketamine, corticosteroids were associated with a reduced risk of POST at the 4 to 6 hours (OR: 0.40, 95% CrI, 0.19-0.83) and 24 hours (OR: 0.34, 95% CrI, 0.16-0.72) time intervals. In addition, during the 2 to 3 hours time interval, *Glycyrrhiza* (OR: 0.38, 95% CrI, 0.15-0.97) was more efficacious than magnesium (Figure 3).

Notable findings from the network contribution plots (Supplemental Digital Content, Appendix 7, http://links.lww.com/AA/D435) were as follows: comparisons of placebo versus *Glycyrrhiza* (13.2%) and versus ketamine (13.2%) had the largest contribution in the entire networks during the 0 to 1 hour time interval; comparisons of the placebo versus NSAIDs (15.7%) and versus ketamine (14.6%) had the largest contribution in the entire networks during the 2 to 3 hours time interval; the comparison of placebo versus *Glycyrrhiza* (14.1%) and versus magnesium (12.5%) had the largest contribution in the entire networks for 4 to 6 hours time interval, and finally, the comparison of placebo versus lidocaine (15.2%) and versus *Glycyrrhiza* (14.6%) had the largest contribution in the entire networks at the 24 hours time interval.

SUCRA and Ranking of All Treatments

Figure 4 shows the SUCRA averages, ranked by different treatment methods in each of the 4 periods

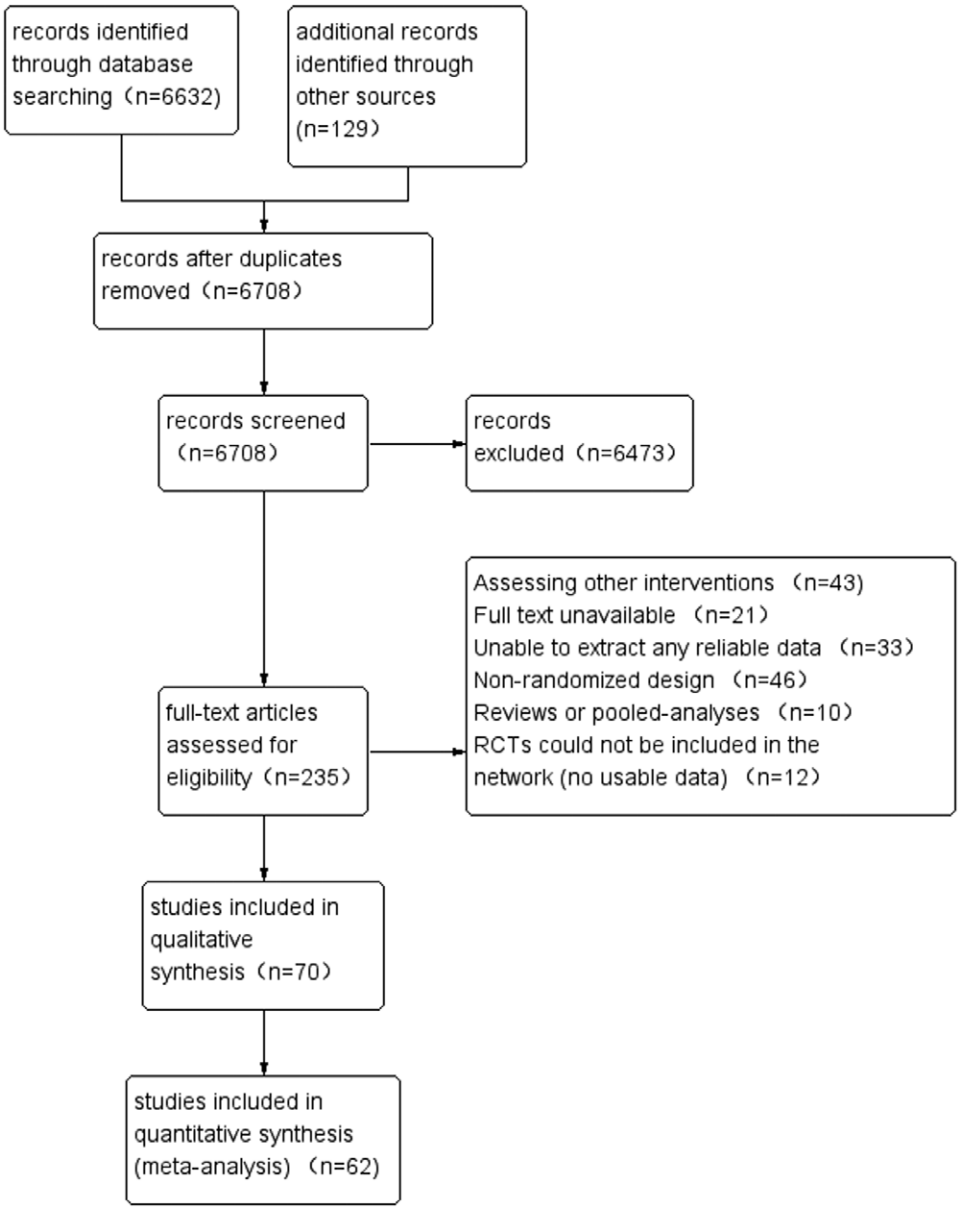

Figure 1. Flow chart of studies reviewed for inclusion. RCT indicates randomized control trial.

(0–1, 2–3, 4–6, and 24 hours). SUCRA data are listed in the treatments for POST symptom improvement ranked, during each respective time interval, as follows: *Glycyrrhiza* ranked second (0–1 hour), first (2–3 hours), second (4–6 hours), and first (24 hours) with the probabilities of 69.1%, 90.2%, 66.3%, and 83.8%, respectively; lidocaine ranked sixth (0–1 hour), fifth (2–3 hours), sixth (4–6 hours), and sixth (24 hours) with the probabilities of 14.6%, 30.1%, 14.6%, and 9.1%, respectively; corticosteroids ranked third (0–1 hour), third (2–3 hours), first (4–6 hours), and second (24 hours) with the probabilities of 68.2%, 68.5%, 97.3%, and 82.7%, respectively; NSAIDs ranked fourth (0–1 hour), second (2–3 hours), third (4–6 hours), and fourth (24 hours) with the probabilities of 67.9%, 69.7%, 60.3%, and 58.3%, respectively; ketamine ranked fifth (0–1 hour), fourth (2–3 hours), fifth (4–6 hours), and fifth (24 hours) with the probabilities of 56.9%, 64.0%, 54.3%, and 35.4%, respectively; finally, magnesium ranked first (0–1 hour), sixth (2–3 hours), fourth (4–6 hours), and third (24 hours) with the probabilities of 71.0%, 27.4%, 54.8%, and 73.0%, respectively.

Examination of Assumptions in the Network Meta-analysis (Transitivity, Consistency, and Heterogeneity)

Assessment of transitivity by box plots indicated that mean age across preventive interventions comparisons were similar (Supplemental Digital Content, Appendix 9, http://links.lww.com/AA/D435). The locally inconsistent test showed that all loops were consistent for outcomes based on 95%

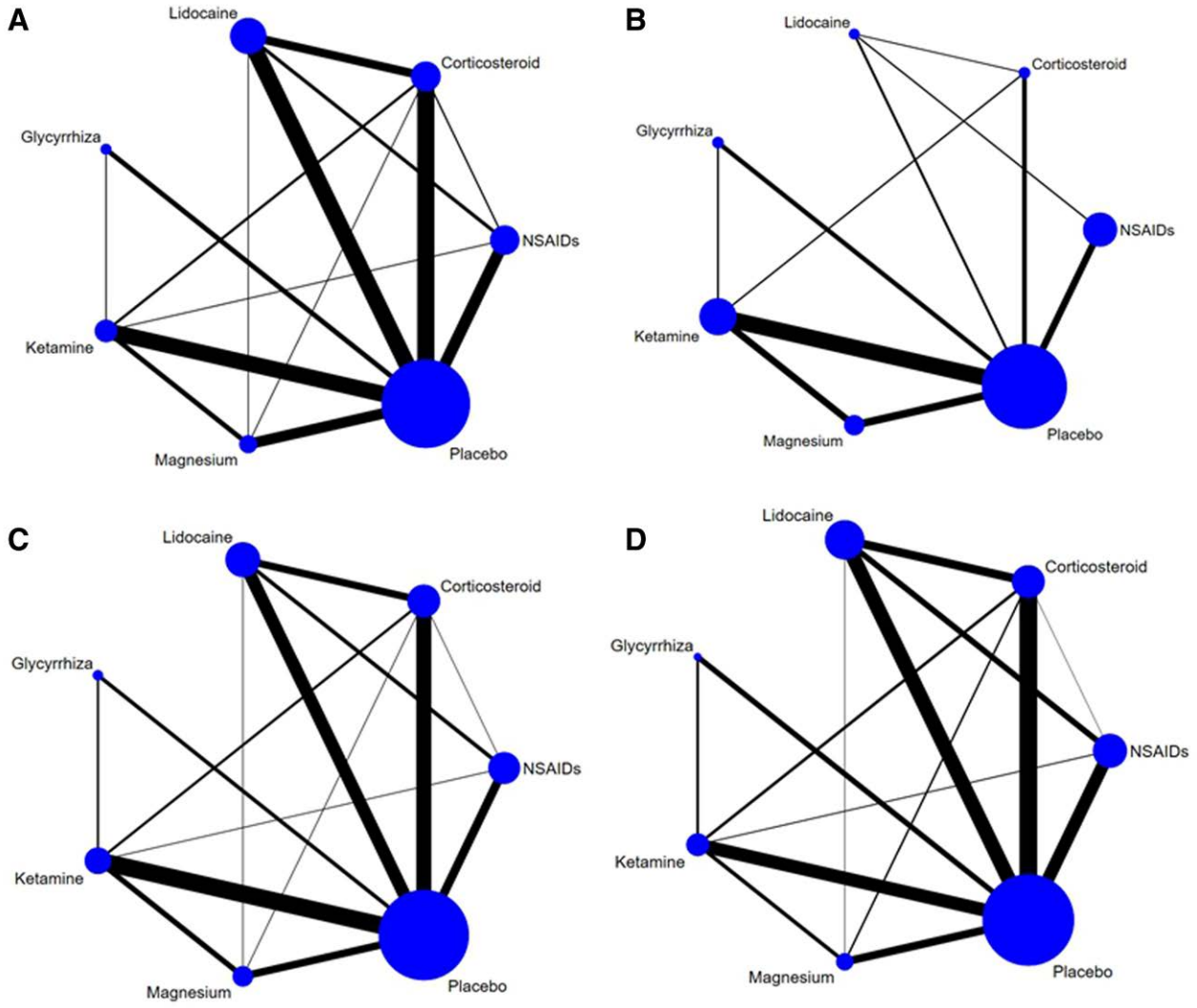

Figure 2. Evidence structure of eligible comparisons for the network meta-analysis. A, 0–1 h. B, 2–3 h. C, 4–6 h. D, 24 h.

CIs including 1 according to the inconsistency plots (Supplemental Digital Content, Appendix 10.1, http://links.lww.com/AA/D435). Inconsistent tests using the node-splitting model demonstrated no significant differences between direct and indirect comparisons for most comparisons within each of the 4 postoperative time intervals (Supplemental Digital Content, Appendix 10.2, http://links.lww.com/AA/D435). All the PSRFs are in the range of 1.00 to 1.14, which indicates that the model converges are complete, the effect of iteration is significant, and the result is stable. Thus, the consistency model is adopted. Predictive interval plots indicated that 33.3%, 0%, 42.8%, and 23.8% of the comparisons for the outcomes at 0 to 1, 2 to 3, 4 to 6, and 24 hours, respectively, were substantially influenced by the estimated heterogeneity in the network (Supplemental Digital Content, Appendix 11, http://links.lww.com/AA/D435).

ROB Assessment

In the visual inspection, the funnel plots of comparisons within each of the 4 time intervals (Supplemental Digital Content, Appendix 12, http://links.lww.com/AA/D435, for comparison-adjusted funnel plot) were relatively symmetrical and showed no significant risk of publication bias in the study samples included.

GRADE Quality Assessment of All Comparisons in the Network

According to GRADE, the quality of evidence ranged between very low and moderate(Supplemental Digital Content, Appendix 14, http://links.lww.com/AA/D435).

DISCUSSION

This study analyzed 62 trials, including a total of 6708 subjects who were randomly assigned to 6 drugs or a placebo to prevent local POST following

A

Corticosteroid						
0.88 (0.42, 1.90)	Ketamine					
0.30 (0.16, 0.55)	0.34 (0.16, 0.69)	Lidocaine				
1.04 (0.37, 2.96)	1.18 (0.43, 3.30)	3.45 (1.27, 9.77)	Glycyrrhiza			
1.04 (0.46, 2.30)	1.17 (0.55, 2.51)	3.45 (1.62, 7.56)	1.00 (0.34, 3.02)	Magnesium		
1.01 (0.48, 2.13)	1.14 (0.55, 2.42)	3.33 (1.70, 6.79)	0.97 (0.33, 2.71)	0.97 (0.42, 2.22)	NSAIDs	
0.23 (0.13, 0.40)	0.26 (0.15, 0.45)	0.76 (0.47, 1.25)	0.22 (0.09, 0.53)	0.22 (0.12, 0.42)	0.23 (0.13, 0.39)	Placebo

B

Corticosteroid						
0.97 (0.43, 2.21)	Ketamine					
0.55 (0.20, 1.35)	0.56 (0.23, 1.33)	Lidocaine				
1.46 (0.47, 4.09)	1.46 (0.62, 3.58)	2.65 (0.94, 8.31)	Glycyrrhiza			
0.55 (0.22, 1.40)	0.56 (0.30, 1.04)	1.00 (0.39, 2.76)	0.38 (0.15, 0.97)	Magnesium		
1.01 (0.43, 2.37)	1.05 (0.57, 1.95)	1.89 (0.81, 4.62)	0.70 (0.29, 1.74)	1.89 (0.90, 3.77)	NSAIDs	
0.19 (0.09, 0.39)	0.20 (0.13, 0.30)	0.35 (0.16, 0.79)	0.13 (0.06, 0.29)	0.35 (0.20, 0.59)	0.19 (0.12, 0.28)	Placebo

C

Corticosteroid						
0.40 (0.19, 0.83)	Ketamine					
0.13 (0.07, 0.25)	0.33 (0.16, 0.68)	Lidocaine				
0.51 (0.16, 1.70)	1.27 (0.41, 4.04)	3.87 (1.20, 12.71)	Glycyrrhiza			
0.41 (0.18, 0.88)	1.01 (0.51, 1.97)	3.08 (1.42, 6.67)	0.80 (0.23, 2.59)	Magnesium		
0.44 (0.21, 0.91)	1.09 (0.53, 2.23)	3.33 (1.67, 6.67)	0.87 (0.26, 2.71)	1.08 (0.48, 2.42)	NSAIDs	
0.10 (0.06, 0.17)	0.24 (0.14, 0.40)	0.74 (0.43, 1.29)	0.19 (0.07, 0.53)	0.24 (0.13, 0.45)	0.22 (0.13, 0.39)	Placebo

D

Corticosteroid						
0.34 (0.16, 0.72)	Ketamine					
0.12 (0.06, 0.21)	0.35 (0.17, 0.72)	Lidocaine				
1.25 (0.28, 5.81)	3.65 (0.84, 17.35)	10.37 (2.35, 48.91)	Glycyrrhiza			
0.83 (0.35, 1.96)	2.42 (1.09, 5.55)	6.88 (2.99, 16.31)	0.66 (0.13, 3.19)	Magnesium		
0.64 (0.31, 1.29)	1.86 (0.88, 3.95)	5.23 (2.72, 10.49)	0.51 (0.11, 2.29)	0.77 (0.32, 1.86)	NSAIDs	
0.12 (0.07, 0.19)	0.34 (0.19, 0.59)	0.96 (0.61, 1.53)	0.09 (0.02, 0.37)	0.14 (0.07, 0.28)	0.18 (0.10, 0.32)	Placebo

Figure 3. Results of the network meta-analysis for the 6 topical pharmacological agents for the preventive interventions of postoperative sore throat in terms of (A) the risk of POST 0–1 h after surgery, (B) the risk of POST 2–3 h after surgery, (C) the risk of POST 4–6 h after surgery, and (D) the risk of POST 24 h after surgery. Results were presented as OR with 95% CrI, and the estimations should read as column-defining treatment compared with the row-defining treatment. The OR < 1 was identified that the column-defining treatment had better effect on preventing POST. CrI indicates credible interval; NSAIDs, nonsteroidal ant-inflammatory drugs; OR, odds ratio; POST, postoperative sore throat.

endotracheal intubation. The investigation included a detailed search of published systematic reviews and head-to-head comparisons. Evidence indicates that the clinical manifestations of POST are self-limiting. Therefore, prevention, rather than treatment, is the best approach to improve the quality of care and patient satisfaction for what is reported to be the eighth worst clinical anesthesia outcome. Our meta-analysis suggests that glycyrrhizin, corticosteroids, NSAIDs, and NMDA receptor antagonists are associated with reduced postoperative pharyngeal pain across the 4 postsurgical time intervals studied. No difference was found between the lidocaine and the placebo during the early extubation, 4 to 6 hours time interval, and 24 hours time interval. These results indicate that 5 of the topical prophylaxis therapies (*Glycyrrhiza*, corticosteroids, NSAIDs, magnesium, and ketamine) are all likely to be effective, while lidocaine is likely the least effective. Slight variations in the calculated rank orders for each drug within each respective different time interval may have arisen from differences in the pharmacological mechanisms and/or the pharmacological composition.[1,25,26]

The mechanism of POST development is thought to be inflammation caused by the traumatic laryngoscopy and ETT cuff injury to the pharynx and trachea mucosa. Drugs with analgesic and anti-inflammatory effects may be the best option for the POST prevention after the ETT intubation under general anesthesia. Previous studies of lidocaine for localized POST prevention have conflicting findings.[27] Adverse effects linked with the use of topical lidocaine in the early postoperative period may increase the overall POST

Treatment	0-1h		2-3h		4-6h		24h	
	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank
Corticosteroid	68. 2 (0. 33, 1. 0)	3	68. 5 (0. 33, 1. 0)	3	97. 3 (0. 83, 1. 0)	1	82. 7 (0. 5, 1. 0)	2
Ketamine	56. 9 (0. 33, 1. 0)	5	64 (0. 33, 1. 0)	4	54. 0 (0. 33, 0. 83)	5	35. 4 (0. 33, 0. 5)	5
Lidocaine	14. 6 (0, 0. 17)	6	30. 1 (0. 17, 0. 83)	5	14. 6 (0, 0. 17)	6	9. 1 (0, 0. 17)	6
Glycyrrhiza	69. 1 (0. 33, 1. 0)	2	90. 2 (0. 5, 1. 0)	1	66. 3 (0. 33, 1. 0)	2	83. 8 (0. 33, 1. 0)	1
Magnesium	71. 0 (0. 33, 1. 0)	1	27. 4 (017, 0. 67)	6	54. 8 (0. 33, 0. 83)	4	73 (0. 5, 1. 0)	3
NSAIDs	67. 9 (0. 33, 1. 0)	4	69. 7 (0. 33, 1. 0)	2	60. 3 (0. 33, 0. 83)	3	58. 3 (0. 33, 0. 83)	4
Placebo	2. 3 (0, 0. 17)	7	0. 0 (0, 0)	7	2. 5 (0, 0. 17)	7	7. 6 (0, 0. 17)	7

Figure 4. Ranking probability of different drugs on postoperative sore throat after the tracheal intubation. Ranking: probability of being the best treatment, of being the second best, the third best, and so on, among all treatments. Rank 1 is best, and rank N is worst. NSAIDs indicates nonsteroidal ant-inflammatory drugs; SUCRA, surface under the cumulative ranking.

incidence to 23% according to 1 study. In addition, lidocaine jelly contains additive preservatives, such as chlorhexidine gluconate, which can cause allergic reactions,[28] and methyl hydroxybenzoate and propyl hydroxybenzoate, which are chemical allergens that can cause allergic dermatitis[29,30] and can also form dry deposits. All of these additives can irritate the respiratory tract and increase coughing and POST incidence. A meta-analysis by the Cochrane collaboration investigating lidocaine use across a variety of different applications and concentrations found no observed benefit when analyses were restricted to studies considered to be of high quality (relative ratio [RR]: 0.71, 95% CI, 0.47-1.09),[31] which is consistent with our findings.

Our findings are also consistent with the results of prior paired meta-analyses, although it should be noted that both direct and indirect comparisons of treatments were included in this network meta-analysis, and some treatments had never previously been directly compared. Licorice is known for its anti-inflammatory and antiallergic properties. Extracted from the roots of *Glycyrrhiza glabra*, licorice contains anti-inflammatory ingredients including glycyrrhizin (glycyrrhizic acid) and glabridins.[17] Glycyrrhizin induces the effects by acting on the adrenal glands, which are responsible for the production of cortisol, an anti-inflammatory adrenal hormone.[32] Glycyrrhizic acid reportedly inhibits cyclooxygenase activity, prostaglandin formation, and platelet aggregation, which thereby impedes the inflammatory process.[33] Kuriyama et al[34] suggest that the preoperative topical application of licorice is associated with the reduced incidence of POST caused by the endotracheal intubation under general anesthesia in adults and that topical licorice may not be associated with major adverse events. Three studies have shown no adverse reactions, and 1 study showed no significant differences between the groups despite the possibility of adverse events.[34] While the long-term systemic use of glycyrrhizae selenium is associated with pseudoaldosteronism, hyperkalemia, and hypertension, short-term adverse events associated with the localized use of glycyrrhizae remain unclear.

Animal experiments indicate that corticosteroids can reduce laryngeal infiltration by inflammatory cells after prolonged intubation.[7] One systematic review found that evidence on the efficacy and safety

of nebulized glucocorticoids is limited and inconclusive.[34] However, we have investigated the effectiveness of corticosteroids from a different perspective.

In terms of NSAIDs, Kuriyama et al[13] show that although data detailing the side effects of NSAIDs are limited, benzylamine does not appear to cause adverse reactions. Regarding NMDA receptor antagonists, 2 RCTs (6 and 54) found magnesium to be more effective than ketamine, consistent with the results of this study. But there are few studies that investigate the safety of magnesium and ketamine administration, calling for more detailed investigation.

Our findings do not come without limitations. First, dosing variations may have impacted study findings. As there were insufficient study subjects and incidents required to form a good network, a presumed dose based on the most common dosing practices was used for the purpose of this analysis. In addition, the most direct comparison showed no substantial inconsistency between our traditional meta-analysis and our network meta-analysis. Second, of the 5 studies, including *Glycyrrhiza*, 3 had only placebo as a comparator and the other 2 were 3-arm studies and included placebo and ketamine. There are no direct comparisons with the other 4 interventions. The high SUCRA ranking for *Glycyrrhiza* is not sufficient to promote the intervention. Based on the findings of this study, it is recommended that future studies should be carried out with the RCTs of direct comparisons between different drugs to overcome the limitations of indirect comparisons. In addition, we did not investigate adverse events due to insufficient publication data that were needed to carry out direct comparisons. Furthermore, the costs of these drugs were rarely discussed in the original literature, and thus, we cannot provide in-depth suggestions regarding the cost of the treatment. Third, the subgroup analyses should be carried out in accordance with operation length. Surgical duration was not reported in most of the studies included in our analysis, preventing us from making this assessment. Despite these limitations, our network meta-analysis provides comparative information derived from one of the largest data sets, and the main findings highlight the current use of different localized prophylactic medications. This investigation used a broader pool of data than previous investigations, making it the most comprehensive study published to date on the prevention of POST caused by the endotracheal intubation under general anesthesia. Therefore, the findings presented here are appropriate for incorporation into clinical practice and relevant guidelines.

CONCLUSIONS

Our analysis shows that, among the 6 topical medications studied, lidocaine is not recommended for topical use in the prevention of POST. Glycyrrhizin, corticosteroids, NSAIDs, and NMDA receptor antagonists are associated with the reduced postoperative pharyngeal pain across the 4 postsurgical time intervals examined. These treatments can be selected depending on the clinical experience of the anesthesiologists or the patient values and preferences for the reduction of postoperative throat pain. ■

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