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REPORTS OF ORIGINAL INVESTIGATIONS

Benzydamine hydrochloride on postoperative sore throat: a meta-analysis of randomized controlled trials

Le chlorhydrate de benzydamine pour les maux de gorge postopératoires: une méta-analyse d'études randomisées contrôlées

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Abstract

Purpose *Sore throat is a common postoperative complaint. The etiology of postoperative sore throat (POST) is considered the result of damage to airway mucosa after insertion of a laryngeal mask airway device or endotracheal tube. This paper proposes benzydamine hydrochloride (BH), a topical nonsteroidal anti-inflammatory drug (NSAID) with additional analgesic and local anesthetic properties, for POST prevention.*

Source *We systematically searched PubMed, EMBASE™, Cochrane, and other relevant databases for randomized controlled trials (RCTs) that investigated the outcome of topical application of BH vs non-application in patients undergoing general anesthesia. Using a random effects model, meta-analyses were conducted to assess the relative risks of the incidence of POST within 24 hr following the surgical procedure. The secondary outcomes included postoperative nausea and vomiting, dry mouth, coughing, and local irritation.*

Principal findings *We reviewed five trials that included 824 patients in total. Our results indicated that the incidence of POST was significantly reduced in the BH group, with risk ratios (RRs) of 0.37 (95% confidence interval [CI]: 0.20 to 0.68) at zero to one hour, 0.39 (95% CI: 0.27 to 0.57) at one to two hours, 0.42 (95% CI: 0.22 to 0.81) at four to six hours, 0.29 (95% CI: 0.10 to 0.88) at six to 12 hr, and 0.32 (95% CI: 0.18 to 0.56) at 12 to 24 hr, compared with the control groups. Patients reported local irritation, but no major BH-related complications were observed.*

Conclusion *Our results indicate that the incidence of POST can be significantly reduced by prophylactic BH topical application to the oral cavity or airway devices. Further RCTs are required to overcome the limitations of heterogeneity and to determine the optimal dosage and application of BH for managing POST.*

Author contributions *Ka-Wai Tam* and *Chien-Yu Chen* devised the study. *Ka-Wai Tam*, *Chien-Yu Chen*, and *Chien-Ju Kuo* extracted, analyzed and interpreted the data. *Ka-Wai Tam* and *Chien-Yu Chen* wrote the first draft. All authors contributed to subsequent versions of the manuscript.

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Résumé

Objectif *Les maux de gorge sont une affection postopératoire courante. On considère l'étiologie du mal de gorge postopératoire comme le résultat d'une atteinte à la muqueuse des voies aériennes après l'insertion d'un masque laryngé ou d'une sonde endotrachéale. Cet article propose d'utiliser du chlorhydrate de benzydamine (CB), un anti-inflammatoire non stéroïdien (AINS) topique disposant en plus de propriétés analgésiques et anesthésiques locales, pour prévenir le mal de gorge postopératoire.*

Source *Nous avons effectué une recherche méthodique dans les bases de données PubMed, EMBASE™, Cochrane, ainsi que dans d'autres bases de données pertinentes pour en tirer les études randomisées contrôlées (ERC) s'intéressant au résultat d'une application topique de CB par rapport à aucune application chez des patients subissant une anesthésie générale. À l'aide d'un modèle à effets aléatoires, des méta-analyses ont été réalisées afin d'évaluer les risques relatifs d'incidence de mal de gorge postopératoire au cours des 24 heures suivant l'intervention chirurgicale. Les critères d'évaluation secondaires comprenaient l'incidence de nausées et vomissements postopératoires, la sécheresse buccale, la toux et l'irritation locale.*

Constatations principales *Nous avons passé en revue cinq études incluant 824 patients au total. Nos résultats ont indiqué que l'incidence de mal de gorge postopératoire était réduite de façon significative dans le groupe CB, avec des risques relatifs (RR) de 0,37 (intervalle de confiance [IC] 95 %: 0,20 à 0,68) de zéro à une heure, 0,39 (IC 95 %: 0,27 à 0,57) de une à deux heures, 0,42 (IC 95 %: 0,22 à 0,81) de quatre à six heures, 0,29 (IC 95 %: 0,10 à 0,88) de six à 12 h, et 0,32 (IC 95 %: 0,18 à 0,56) de 12 à 24 h, par rapport aux groupes témoin. Les patients ont rapporté une irritation locale, mais aucune complication majeure liée au CB n'a été observée.*

Conclusion *Nos résultats indiquent que l'incidence de mal de gorge postopératoire peut être réduite de façon significative en utilisant du CB prophylactique en application topique à la cavité orale ou aux dispositifs d'intubation. Des ERC supplémentaires sont nécessaires pour surmonter les limites causées par l'hétérogénéité des résultats et pour déterminer la posologie et l'application optimales de CB pour la prise en charge des maux de gorge postopératoires.*

Postoperative sore throat (POST) is a minor adverse result of general anesthesia that affects patient satisfaction as well as the quality of care, especially in ambulatory surgical patients.[1-3] Patients rank POST as the eighth most undesirable outcome after surgical procedures.[2] The incidence of POST is remarkably high, varying from 21-66%.[1,4-6] The etiology of POST is multifarious and obscure.[1,5,6] Postoperative sore throat may be caused by any mucosa injury during intubation or extubation of the endotracheal tube (ETT), insertion of a laryngeal mask airway device (LMAD), inflation of an airway device, suction of secretions, mask ventilation, or the application of cricoid pressure.

Due to the diverse etiology of POST, various therapeutic or prophylactic management strategies exist. In the past two decades, some causal factors of POST have been identified, and various POST prevention strategies have been implemented in clinical settings. Airway devices, insertion techniques, the use of a lubricant, airway designs, cuff pressures, the length and type of surgical procedure, the anesthetics administered, and evaluation techniques have all been considered.[1,4,7]

Increasingly more investigators have turned their focus from non-pharmacological to pharmacological interventions in their efforts to attenuate POST.[3] For example, lidocaine was traditionally used to protect tracheal intubated adults against POST. We propose benzydamine hydrochloride (BH), a topical nonsteroidal anti-inflammatory drug (NSAID) with additional analgesic and local anesthetic properties, for POST prevention.[8,9]

Several randomized controlled trials (RCTs) have investigated the analgesic efficacy of BH on POST, but the results have been inconclusive.[4-6,10] Therefore, we conducted a systematic review and meta-analysis of the available evidence to date regarding patient outcomes where BH was administered to patients undergoing general anesthesia.

Methods

This article reports our meta-analysis of RCTs of BH compared with placebo for prevention of POST in accordance with the PRISMA guideline and AMSTAR rating scale.[11,12] A review protocol was written prior to conducting the study.

Inclusion criteria

Two reviewers screened all articles and abstracts jointly and independently for the following inclusion criteria: 1) a RCT; 2) evaluation of BH outcomes in patients undergoing general anesthesia; and 3) inclusion of any outcome of interest (the incidence and severity of POST or drug-related complications). Previous RCTs were excluded from our meta-analysis based on the following criteria: 1)

emergency operations; 2) surgical procedures involving the head and neck; 3) patients younger than 18 yr; 4) the appropriate data could not be extracted or calculated from the published results; or 5) duplicate reporting of patient cohorts.

Search strategy and study selection

We performed a comprehensive literature search in several databases, including PubMed, EMBASE™, Scopus™, the Cochrane central registers of controlled trial databases, and the ClinicalTrials.gov registry (http://clinicaltrials.gov/). The keywords used for the medical subject heading and free text searches were: *postoperative sore throat*, *pharyngeal morbidity*, *pharyngeal discomfort*, *pharyngeal complication*, *airway morbidity*, *airway discomfort*, *airway complication*, *pain,, throat morbidity*, *throat discomfort*, *throat complication*, *benzydamine*, *benzydamine hydrochloride (BH)*, or *non-steroidal anti-inflammatory drugs (NSAIDs)* (Appendix). The related citations in the PubMed search tool were used to broaden each search, and we reviewed all the abstracts, study reports, and related citations that were retrieved. We hand-searched abstracts of selected conferences from 2003-2013, including those of the American Society of Anesthesiologists, the Canadian Anesthesiologists' Society, and the International Anesthesia Research Society. No language restrictions were imposed. The last search was performed in August 2013.

Data extraction

Two reviewers independently extracted the baseline and outcome data, including the study design, the participant data, the inclusion and exclusion criteria, the anesthetic techniques used, the airway devices used, and any resulting complications. A third reviewer resolved any inconsistencies between the findings of the two reviewers.

Methodological quality appraisal

We assessed the methodological quality of each study based on the adequacy of the randomization, the allocation concealment, the blinding of the patients and the outcome assessors, the length of the follow-up period, the reporting of study withdrawals, the performance of an intention-to-treat analysis, and other possible sources of bias.

Outcomes and statistical analysis

The primary outcome was the incidence and severity of POST within 24 hr post-operation. The secondary outcomes included drug-related complications such as the incidence of postoperative nausea or vomiting, coughing, dry mouth, numbness, or a stinging sensation. All data were entered and analyzed using the Review Manager (RevMan), version 5 (Cochrane Collaboration, Oxford, England). When necessary, standard deviations were estimated from the confidence interval (CI) limits, the standard error, or the range values provided in the previous studies. The effect sizes of dichotomous outcomes were reported as risks ratios (RR), and the mean difference was reported for continuous outcomes. The precision of the effect sizes was based on a 95% CI. A pooled estimate of the RR was computed by the DerSimonian and Laird random-effects model.[13] This model gives an appropriate estimate of the average treatment effect when trials are statistically heterogeneous, and it usually yields relatively wide CIs, resulting in a more conservative statistical claim.

To evaluate the statistical heterogeneity and the inconsistency of treatment effects across the studies, the Cochrane Q test and I^2 statistics were used, respectively. Statistical significance was set at .10 for the Cochrane Q tests. The proportion of the total outcome variability that was attributable to the variability across the studies was quantified as I^2. Sensitivity analyses were performed to assess any impact of study quality on the effect estimates. Subgroup analyses were also performed by pooling estimates for similar subsets of patients across trials where available. The Egger test was used to assess the funnel plot for significant asymmetry, indicating possible publication or other bias.[14]

Results

Trial characteristics

Five RCTs involving 824 participants met the inclusion criteria. The flowchart in Fig. 1 shows the process that was used to screen and include RCTs. Our initial search yielded 1,373 citations. Based on the screening criteria for titles and abstracts, 1,105 were excluded. After reviewing the full text of the remaining 268 reports, only five eligible RCTs fit our inclusion criteria and were selected for the study.[4-6,10,15] These five studies were all published in English during 2004-2010, and the sample size ranged from 40-380 patients. All trials recruited patients with American Society of Anesthesiologists (ASA) status I-III undergoing general anesthesia with ETT intubation[4-6,10] or insertion of a laryngeal mask airway device[15] for non-emergency operations that did not involve head and neck surgery. A topical BH application group was compared with a control group in all trials. One study also compared the preventive effects of acetylsalicylic acid with those of BH on POST.[4] A second trial adopted dexpanthenol pastille and BH spray for sore throat prevention.[5]

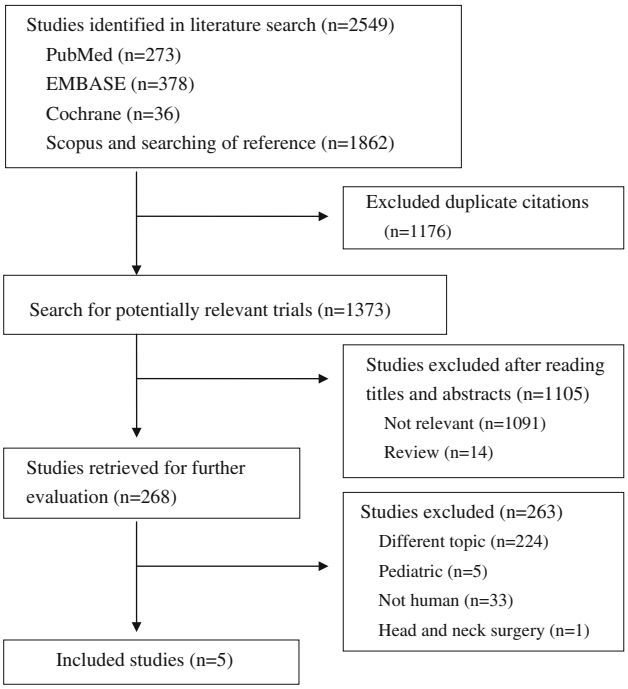

Fig. 1 A flowchart describing the selection of the randomized controlled trials for our meta-analysis

Another study investigated various dosages of lidocaine.[10] In four studies, BH was sprayed directly to either the ETT[6,10] or the oropharyngeal cavity,[5,6,15] or both.[6] In one trial, BH was gargled rather than sprayed.[4] The dosages of direct BH spray varied from five to ten puffs (0.75-2.16 mg), whereas the gargled dosage was 22.5 mg. Two trials chose to apply the medication twice instead of once before induction.[5,15] The patient characteristics, anesthetic techniques, and surgical procedures used in each of the five trials are shown in Table 1.

Our assessment of the methodological quality of the five selected RCTs is summarized in Table 2. Four studies have used acceptable methods of randomization,[4,5,10,15] and two studies clearly described the method of allocation concealment.[4,10] All studies except one reported the blinding of the patients, clinicians, and the outcome assessors.[4] Two studies performed an intention-to-treat analysis, and none of the patients withdrew during the follow-up periods.[5,15] Other biases included a significant difference in the taste of the experimental drugs,[4] and one study did not define the BH dosage.[15]

Incidence of POST

All five RCTs have evaluated both the incidence and severity of sore throat through face-to-face interviews within 24 hr post-operation. Nevertheless, the severity of sore throat was not extracted and pooled in this study due to the disparity among the grading systems adopted. Since different times were used for the assessment of POST, we arranged the outcomes into five subgroups: zero to one hour, one to two hours, four to six hours, six to 12 hr, and 12 to 24 hr. In one RCT, the BH group was nearly triple the size of the control group because all three of its experimental groups fit our recruitment criteria.[6]

Figure 2 shows significant differences between the BH and control groups in all six time groups. The incidence of POST was significantly reduced in the BH group, and the RRs were 0.37 (95% CI: 0.20 to 0.68) at zero to one hour, 0.39 (95% CI: 0.27 to 0.57) at one to two hours, 0.42 (95% CI: 0.22 to 0.81) at four to six hours, 0.29 (95% CI: 0.10 to 0.88) at six to 12 hr, and 0.32 (95% CI: 0.18 to 0.56) at 12 to 24 hr. The values of I^2 were 74%, 10%, 85%, 69%, and 26% for the five the respective subgroups, indicating that moderate heterogeneity existed across the studies.

For evaluation of publication bias, the incidence of POST in the BH groups and control groups was plotted against precision groups using a funnel plot. A limb missing was found in the funnel plot indicating a potential for publication bias (Fig. 3).

Incidence of complications

All five studies evaluated the incidence of complications. Figure 4 shows that there were no major BH-related complications (e.g., nausea, vomiting, dry mouth, or coughing), and only minor complaints of a strange taste or sensation (e.g., local numbness or stinging) were ascertained when BH was applied. The incidence of numbness or stinging was significantly increased in the BH group, with an RR of 6.37 (95% CI: 1.51 to 26.94).

Sensitivity and subgroup analysis

A sensitivity analysis including only trials with low methodological quality (i.e., inadequate description of the randomization and allocation concealment) and omitting data of Huang *et al.* from the data set showed no significant difference in the incidence of POST and complications.[6] Moreover, the association between BH and POST outcomes remained unchanged among the subgroups by route of delivery (gargling *vs* spraying), times of topical use (twice *vs* once), or ASA status (I-II *vs* I-III) and showed no major differences.

Discussion

This study systematically reviewed and evaluated the preventive effects of the topical application of BH for POST. Our results indicate that the incidence of POST can

Table 1 Characteristics of the selected randomized controlled trials

Study	Patient number (male %)	Airway management	Surgery/ ASA status	Anesthetic technique	Intervention
Agarwal *et al.*	BH: 19 (0) A: 19 (0) C: 20 (0)	ETT 7 mm with 18-22 cmH_2O intubated by anesthesia registrar	Elective MRM/ ASA I-II	Induced by fentanyl 3 $\mu g \cdot kg^{-1}$, propofol 2 $mg \cdot kg^{-1}$, vecuronium 0.1 $mg \cdot kg^{-1}$; maintained by 70% N_2O, 50% O_2, propofol infusion 50-150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with intermittent fentanyl & vecuronium as required.	Gargle after arrival in OR BH: 15 mL (22.5 mg) + D/W 15 mL A: 350 mg + D/W 15 mL C: M/W 15 mL + D/W 15 mL
Gulas *et al.*	BH: 60 (18) D: 60 (32) C: 60 (27)	ETT 8 mm (M) or 7 mm (F) with 20-25 mmHg intubated by R2	Elective surgery/ ASA I-II	Induced by propofol 2-2.5 $mg \cdot kg^{-1}$, vecuronium 1 $mg \cdot kg^{-1}$; maintained by 60% N_2O, 40% O_2, 1.5-2% sevoflurane, yet opioids uncontrolled.	Oral spray 30 min prior to arrival in OR and 5 min before induction BH: 8 puffs (2.16 mg) D: 2 pastilles sucked orally C: D/W 8 puffs
Huang *et al.*	BH_1: 95 (52) BH_2: 95 (47) BH_3: 94 (47) C: 94 (47)	ETT 7 mm (M) or 6.5 mm (F) with 20-25 cmH_2O intubated by R3 or senior doctor	Elective surgery/ ASA I-II	Induced by fentanyl 2-3 $\mu g \cdot kg^{-1}$, lidocaine 1-1.5 $mg \cdot kg^{-1}$, propofol 2-2.5 $mg \cdot kg^{-1}$, rocuronium. 0.6 $mg \cdot kg^{-1}$; maintained by 8-12% desflurane, O_2 total flow 300 $mL \cdot min^{-1}$ with intermittent fentanyl and vecuronium as required.	Oropharyngeal and/or ETT spray 5 min before induction BH_1: 5 puffs (0.75 mg) BH_2: 5 puffs (0.75 mg) BH_3: 5 puffs (oral) + 5 puffs (ETT) (1.5 mg) C: D/W 5 puffs (0.15 mL)
Hung *et al.*	BH: 94 (48) L10: 93 (52) L2: 92 (50) C: 93 (52)	ETT 7.5 mm (M) or 7 mm (F) with 20 cmH_2O intubated by R3 or senior doctor	Surgery with supine position/ ASA I-III	Induced by fentanyl 2-3 $\mu g \cdot kg^{-1}$, propofol 2-2.5 $mg \cdot kg^{-1}$, rocuronium 0.6 $mg \cdot kg^{-1}$; maintained by TCI system with propofol with intermittent fentanyl and rocuronium/cisatracurium as required.	ETT spray 5 min before induction BH: 10 puffs (1.5 mg) L10: 10 puffs (100 mg) L2: 10 puffs (20 mg) C: NS 10 puffs (0.3 mL)
Katı *et al.*	BH:50 (62) C:50 (68)	LMAD size 3-5	Lower extremity and inguinal region/ ASA I-II	Induced by fentanyl 1-2 $\mu g \cdot kg^{-1}$, propofol 2.5-3.5 $mg \cdot kg^{-1}$; maintained by 50% N_2O, 50% O_2, 1-1.5% sevoflurane, fentanyl 50 μg every 30 min	Posterior pharyngeal spray 30 min before OP and 5 min before induction BH: 8 puffs (2.16 mg) C: D/W 8 puffs

A = acetylsalicylic acid; ASA = American Society of Anesthesiologists; BH = benzydamine hydrochloride (0.15%); BH_1 = BH oral spray; BH_2 = BH ETT; BH_3 = BH oral spray + ETT; C = control group; D = dexpanthenol pastille; D/W = distilled water; ETT = endotracheal tube; L10 = lidocaine 10%; L2 = lidocaine 2%; LMAD = laryngeal mask airway device; MRM = modified radical mastectomy; M/W = mineral water; NS = normal saline; OP = operation; OR = operating room; R = resident; TCI = target-controlled infusion

Table 2 Methodological quality assessment of selected trials

Study	Country	Allocation generation	Allocation concealment	Blinding	Loss of follow-up (%)	Data analysis	Other biases
Agarwal *et al.*	India	Computer-generated	Adequate	Assessor blinded	2.5	PP	Obvious taste differences of experimental drugs
Gulas *et al.*	Turkey	Number table	Unclear	Triple	0	ITT	Unclear
Huang *et al.*	Taiwan	Unclear	Unclear	Triple	1	PP	Unclear
Hung *et al.*	Taiwan	Sealed envelopes	Adequate	Triple	11	PP	Unclear
Katı *et al.*	Turkey	Randomized sequence	Unclear	Triple	0	ITT	Unclear

ITT = intention-to-treat; PP = per-protocol

be diminished by applying BH in the oral cavity or on the ETT cuff without causing adverse BH-related effects, except for local irritation.

A Cochrane Review examined the efficacy and risks of other prophylactic and topical drugs, e.g., systemic lidocaine used prophylactically, to prevent POST in

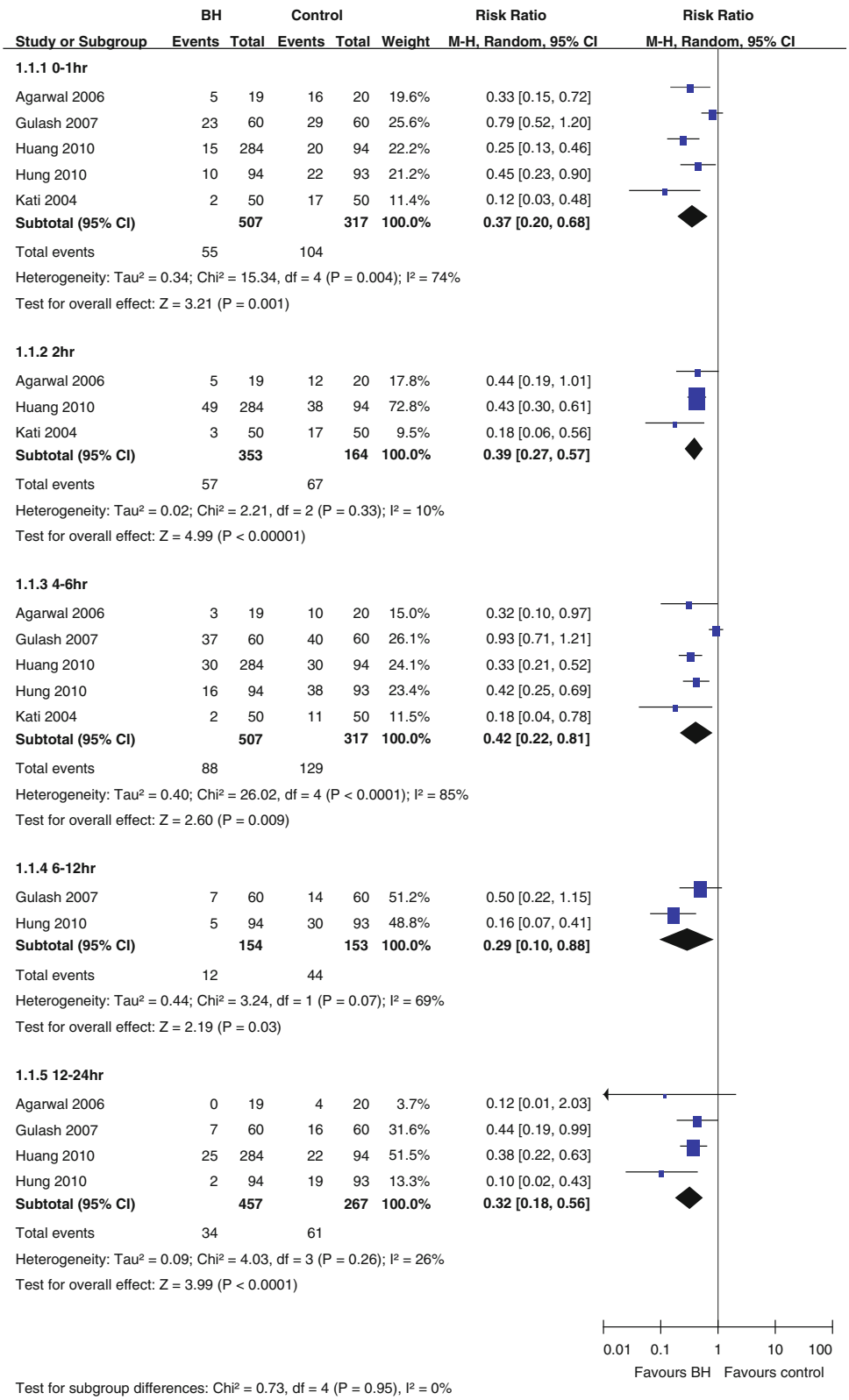

Fig. 2 A forest plot comparing the BH and control groups and showing the incidence of POST at zero to one hour, one to two hours, four to six hours, six to 12 hr, and 24 hr.
BH = benzydamine hydrochloride;
POST = postoperative sore throat

adults undergoing general anesthesia with ETT intubation.[7] The risk and severity of POST tended to be reduced in the lidocaine group. In our included trials, one study compared the effectiveness of lidocaine with that of BH, showing a significantly lower incidence of POST in the BH group than in either the 10% or the 2% lidocaine groups ($P < 0.05$).[10] Another study compared the efficacy of gargling acetylsalicylic acid with that of BH, and results

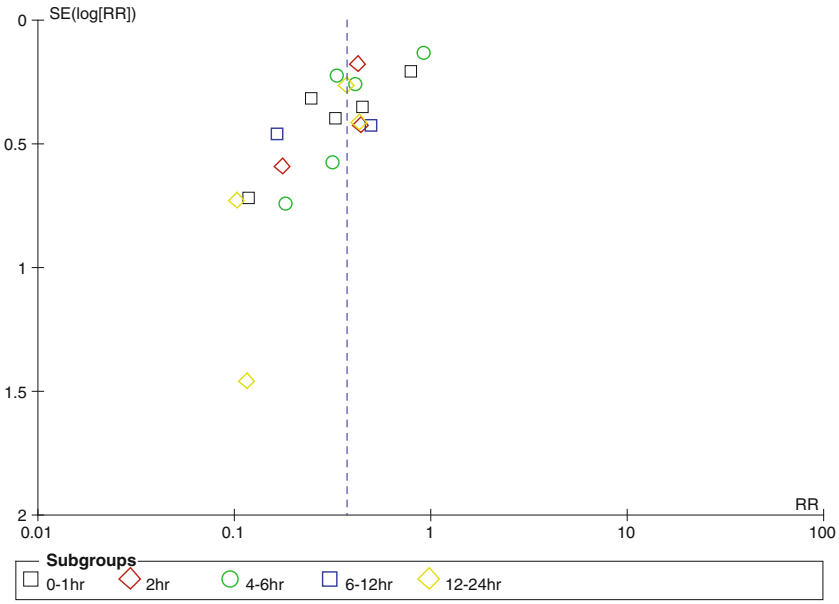

Fig. 3 Funnel plot for the BH and control groups showing the incidence of POST at zero to one hour, one to two hours, four to six hours, six to 12 hr, and 24 hr. BH = benzydamine hydrochloride; POST = postoperative sore throat

showed that the acetylsalicylic acid gargle prevented POST for only two hours, whereas a BH gargle prevented POST for 24 hr.[4] One RCT compared a dexpanthenol pastille with BH sprayed in the oral cavity, and results showed that BH was less effective than the dexpanthenol pastille.[5] Other effective pharmacological methods to decrease the incidence of POST have also been reported in the past, such as transdermal ketoprofen,[16] diclofenac epolamine patch,[17] and tenoxicam-impregnated pharyngeal pack.[18]

Local irritation, such as numbness and a burning or stinging sensation, was found to have increased significantly in the BH group in this study. Nevertheless, unlike other adverse effects specified by patients after a surgical procedure, such complaints occurred in the preoperative period between the topical application of BH and the induction of anesthesia.[4,6,15] To avoid this drawback, Huang *et al*. suggested that BH be applied to the ETT cuff instead of the oropharyngeal cavity.[6]

Investigations on the optimal dose, application, and timing for topical BH application have not been conclusive. Although results show no significant differences in the distribution of gargles and sprays in the oropharynx,[19] BH absorption, peak plasma concentrations, and analgesic efficacy may vary with different topical use.[9] A higher concentration or a larger dosage of BH may not be more effective in preventing POST.[5] Spraying BH in the oropharyngeal cavity or on the ETT cuff caused no significant change in the incidence of POST ($P = 0.088$).[6] Moreover, providing supplemental spray 30 min prior to arrival in the operating room did not result in any benefits.[5,15]

The significant heterogeneity among our selected studies was attributable to various factors. First, the characteristics of the participants varied. In two studies, the female participants were highly dominant,[4,5] and only one trial included patients in ASA class III.[10] Second, the surgical and anesthetic interventions adopted were not identical across all studies. Apart from the disparity between the airway device inserted,[15] other clinical factors, such as opioid dosages, the size of the ETT, the experience level of the anesthesiologists, and the use of nitrous oxide, also exaggerated the heterogeneity of this study. Third, the outcome measure of POST was not totally standardized. The presence of POST manifested in the studies recruited may range from a mild complaint only during swallowing to a severe complaint associated with other morbidities. Finally, the quality of methodology also played a role in the existence of heterogeneity. Sensitivity analysis showed that the values of I^2 were slightly decreased from 74-71% at zero to one hour and from 85-82% at four to six hours.

Our research has limitations. First, the sample sizes used in some of the RCTs were relatively small. Although a meta-analysis can compensate for this limitation to a certain extent, the statistical power of the results remains limited. Second, since the mode of delivery and the dose of BH varied significantly in the five studies included, the inference is still unsettled. Third, BH is not part of common practice in Western countries, and all five trials were conducted in Asia; thus, both the effectiveness and applicability of BH in POST prevention in Western countries remains unknown. Fourth, several studies did not report the details of the sequence generation and

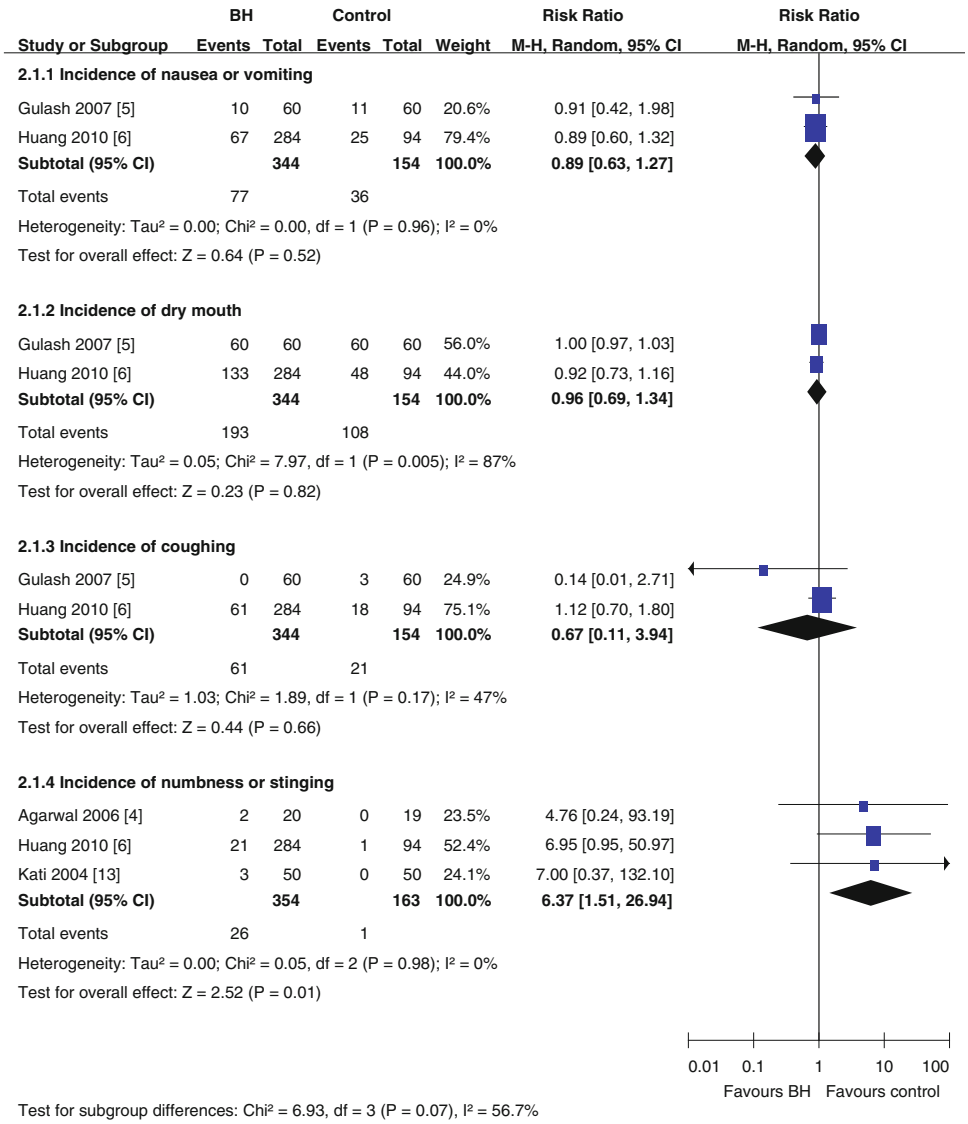

Fig. 4 A forest plot comparing the BH and control groups and showing the incidence of complications, including nausea, vomiting, dry mouth, coughing, and local irritation. BH = benzydamine hydrochloride

allocation concealment. Fifth, several of our secondary outcomes were also secondary outcomes in the RCTs that were variably reported, potentially limiting inferences based on our analysis.

In conclusion, our meta-analysis ascertained the effectiveness of applying prophylactic topical BH to either oral cavities or airway devices for POST prevention. Although such interventions may cause local irritation, this minor complication is limited to the preoperative period. A well-designed and powered RCT would be necessary to examine the efficacy of varying dosages and applications of BH for POST prevention and to help anesthesiologists improve patient postoperative care.

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Conflicts of interest None declared.

Appendix

Searches Benzydamine / NSAID / POST & Related Terms Component
1. exp Anti-inflammatory Agents, non-steroidal/
2. benzydamine OR tantum verde OR difflam.mp
3. 1 OR 2
4. exp Pharyngitis/
5. exp Intubation-intratracheal/
6. (sore* OR inflamm* OR infect*) near throat
7. Pharyngit*
8. (endotracheal OR intratracheal) near intub*
9. Airway near (discomfort OR morbidity OR complication)
10. 4 OR 5 OR 6 OR 7 OR 8 OR 9
11. pain* OR analgesi*.mp

Appendix continued

Searches Benzydamine / NSAID / POST & Related Terms Component
12. randomized controlled trial.pt
13. controlled clinical trial.pt
14. randomized.ab
15. placebo.ab
16. drug therapy.fs
17. randomly.ab
18. trial.ab
19. groups.ab
20. OR/11-18
21. 3 AND 10 AND 20

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