A Randomized, Double-Blind Comparison of Licorice Versus Sugar-Water Gargle for Prevention of Postoperative Sore Throat and Postextubation Coughing

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BACKGROUND: One small study suggests that gargling with licorice before induction of anesthesia reduces the risk of postoperative sore throat. Double-lumen tubes are large and thus especially likely to provoke sore throats. We therefore tested the hypothesis that preoperative gargling with licorice solution prevents postoperative sore throat and postextubation coughing in patients intubated with double-lumen tubes.

METHODS: We enrolled 236 patients having elective thoracic surgery who required intubation with a double-lumen endotracheal tube. Patients were randomly assigned to gargle 5 minutes before induction of anesthesia for 1 minute with: (1) Extractum Liquiritiae Fluidum (licorice 0.5 g); or (2) Sirupus Simplex (sugar 5 g); each diluted in 30 mL water. Sore throat and postextubation coughing were evaluated 30 minutes, 90 minutes, and 4 hours after arrival in the postanesthesia care unit, and the first postoperative morning using an 11-point Likert scale by an investigator blinded to treatment.

RESULTS: The incidence of postoperative sore throat was significantly reduced in patients who gargled with licorice rather than sugar-water: 19% and 36% at 30 minutes, 10% and 35% at 1.5 hours, and 21% and 45% at 4 hours, respectively. The corresponding estimated treatment effects (relative risks) were 0.54 (95% CI, 0.30–0.99, licorice versus sugar-water; $P = 0.005$), 0.31 (0.14–0.68) ($P < 0.001$), and 0.48 (0.28–0.83) ($P < 0.001$).

CONCLUSION: Licorice gargling halved the incidence of sore throat. Preinduction gargling with licorice appears to be a simple way to prevent a common and bothersome complication.   (Anesth Analg 2013;117:614–21)

Postoperative sore throat is a common and annoying complication of endotracheal intubation.[1] Intubation with double-lumen tubes, which are much larger than conventional single-lumen tubes, are especially likely to provoke sore throats, with a reported incidence up to 90%.[2,3] Presumably, postoperative sore throats are a consequence of local tissue trauma, due to laryngoscopy and/or endotracheal intubation, leading to inflammation of pharyngeal mucosa.[4]

Nonpharmacological methods for preventing an intubation-related sore throat include using smaller-sized endotracheal tubes, lubricating the endotracheal tube with water-soluble jelly, careful airway instrumentation, intubation after full relaxation, gentle oropharyngeal suctioning, minimizing cuff pressure, and extubation in deeper planes of anesthesia and with a fully deflated tracheal tube cuff.[5]

Pharmacological measures for attenuating postoperative sore throats include inhalation of beclomethasone[6] or fluticasone propionate[7]; gargling with azulene sulfonate,[8] aspirin,[4] or ketamine[9]; gargling[4] or spraying[10] benzydamine hydrochloride on the endotracheal cuff; IV dexamethasone[2]; oral clonidine[11]; topical or systemic lidocaine[12]; and ingestion of strepsils tablets.[13] Each of these approaches has, however, limitations and variable success rates; thus none has become established or is in routine clinical use.

Recently, Agarwal et al.[14] reported that gargling with licorice halves the risk of sore throat after intubation with conventional endotracheal tubes, based on a study of just 40 patients. A number of active ingredients have been isolated from licorice (glycyrrhiza glabra), including glycyrrhizin, glycyrrhizic acid, liquilitin, liquiritigenin glabridin, and hispaglabridins.[15] The glycyrrhizin component reportedly has anti-inflammatory and antiallergic properties. For example, glycyrrhizic acid retards inflammatory processes by inhibiting cyclooxygenase activity, prostaglandin formation, and platelet aggregation.[16] Liquilitin and liquiritigenin have peripheral and central antitussive properties.[17] Glabridin has significant antioxidant and ulcer-healing properties, which might help heal pharyngeal and tracheal mucosa after minor injuries that often complicate laryngoscopy, intubation, and endotracheal tube cuff inflation.[18] We thus tested the hypothesis that gargling with licorice solution immediately before induction of anesthesia prevents sore throat and postextubation coughing in patients intubated with double-lumen tubes.

METHODS

The study was approved by the local Ethics Committee of the Medical University of Vienna (Ref. 2010/332). According to the Declaration of Helsinki, the approval was published in the publicly accessible register of the Ethics Committee of the Medical University of Vienna (http://ethikkommission.meduniwien.ac.at/register) and registered at ClinicalTrials.gov (identifier: NCT01444703). This study was financed by department and university funding.

After receiving informed written consent, at least a day before surgery, we enrolled 236 adult patients undergoing elective thoracic surgery requiring a double-lumen endotracheal tube. Patients were enrolled at the General Hospital of Vienna between October 2010 and May 2011. All patients were designated ASA physical status I to III and were aged 18 to 90 years; immediate postoperative extubation was planned in each case. The patients were told that the study involved 2 different sweet solutions for prevention of postextubation sore throat.

Exclusion criteria were tracheal pathology including tracheostomy, surgery within the previous month, upper respiratory tract infection, body mass index exceeding 40 kg/m^2, known or suspected allergy to licorice, use of nonsteroidal anti-inflammatory drug medication within 24 hours, chronic opioid use, preoperative pain ≥2 on an 11-point Likert scale (0 = no pain; 10 = worst pain), and known or suspected difficult airway.

Protocol

Patients were premedicated 2 hours before surgery with up to 7.5 mg oral midazolam, per routine. Patients were randomly assigned to 1 of 2 groups: (1) Extractum Liquiritiae Fluidum (licorice 0.5 g); or, (2) Sirupus Simplex (sugar 5 g), which is a solution with a similar degree of sweetness.

Randomization (1:1) to licorice or placebo was assigned by a Web-based system that was accessed just before treatment by an independent researcher who was not involved in data collection; no stratification was used.

Licorice or sugar (placebo) was diluted in 30 mL water and placed in small brown opaque bottles by an independent apothecary. The respective bottles were opened just before use; the investigator was blinded to the preparation used for gargling, and the patient was not told which solution was provided. Patients were asked to gargle at least 1 minute in sitting position, but without swallowing, under supervision and direct observation of a researcher who was not subsequently involved in data collection.

Five minutes after gargling, general anesthesia was induced with fentanyl approximately 3 µg/kg, propofol approximately 1.5 mg/kg, and rocuronium approximately 0.6 mg/kg. After complete neuromuscular block, which was confirmed by absence of palpable twitches in response to supramaximal train-of-four stimulation of the ulnar nerve at the wrist, direct laryngoscopy was performed with a Macintosh laryngoscope, and the trachea was intubated as gently as possible by experienced physicians. We used a 37-cm left-sided unlubricated double-lumen tube for women and a 39-cm left-sided unlubricated double-lumen tube for men. The double-lumen tubes we used did not have a hook; they were inserted with a stylet which was removed as soon as the tube passed the vocal cords. The endotracheal tube cuff was inflated with air to 20 mm Hg immediately after intubation with a standard syringe. Cuff pressure was measured immediately after inflation and again after patients were positioned laterally, and adjusted as necessary to maintain pressure at 20 mm Hg.

General anesthesia was maintained with sevoflurane, and patients' lungs were ventilated with oxygen and air as deemed appropriate by the attending anesthesiologist. End-tidal P_{CO_2} was maintained between 32 and 35 mm Hg to the extent clinically practical. Hypnotic depth was guided by the Bispectral Index (Covidien, Dublin, Ireland), targeted between 40 and 50.

Small amounts of opioid were given per clinical judgment. At the end of surgery, an intercostal plexus block, using up to 20 mL ropivacaine 0.1%, was performed by the thoracic surgeon who was otherwise not involved in this study. Paracetamol, 1000 mg, was given IV 10 minutes before end of surgery. Patients were tracheally extubated, while still anesthetized, after confirmation of adequate spontaneous breathing and 4 twitches in response to supramaximal train-of-four stimulation of the ulnar nerve at the wrist. Postoperative pain was treated using fractional piritramid (Dipidolor) 3 mg IV as required.

Measurements

Thirty minutes and 1.5 hours after arrival in the postanesthesia care unit (PACU), and 4 hours after extubation, sore throat using an 11-point Likert scale (0 = no pain; 10 = worst pain) was assessed. Thirty minutes after arrival in the PACU, pain with swallowing was assessed with the same 11-point Likert scale. Sore throat was defined as a visual analog scale score exceeding 0.

Postextubation coughing was assessed by clinical observation and questioning the patient immediately after extubation, 0.5 and 1.5 hours after arrival in the PACU and 4 hours after extubation. We used an established scoring system: (1) none; (2) mild (less than a common cold); (3) moderate (similar to a common cold); and (4) severe (more than a common cold).[19]

Patients were asked whether they experienced any side effects related to the use of the gargle solution, including allergic reactions, discomfort, and mucosal burning. All examinations in the PACU were performed by the same independent, blinded, and experienced nurses who were not present when the patient gargled and were not involved in anesthetic management. On the first postoperative morning, sore throat pain and coughing were assessed, again by an independent and blinded investigator by clinical observation and questioning the patient using the scoring systems mentioned above.

Statistical Analysis

The 2 randomized groups (licorice and sugar-water) were compared for balance on demographics and baseline characteristics using standard summary statistics and the standardized difference (STD), defined as the difference in means or proportions divided by the pooled standard deviation. We prespecified a criterion of >0.20 absolute STDs as an indication of imbalance. All analyses were conducted on the conservative intention-to-treat basis.

Primary Analysis

The primary aim of the study was to assess the effect of licorice gargle on the occurrence of sore throat at rest after intubation with double-lumen endotracheal tubes compared with sugar-water gargle after surgery through the first 4 postextubation hours (i.e., measured at 0.5 and 1.5 hours after arrival in the PACU and 4 hours after surgery). The overall treatment effect across the 3 measurements was our primary analysis, with use of the modified Mantel-Haenszel test adjusting for the within-patient correction.[20]

Secondary Analyses

We assessed the effect of licorice on the incidence of sore throat at rest assessed at postoperative day (POD) 1 morning, and the incidence of sore throat during swallowing assessed at 0.5 hours after arrival in the PACU using χ^2 tests.

The overall mean difference in the sore throat pain between licorice and sugar-water groups across the 2 conditions (i.e., at rest and during swallowing) at 0.5 hours after arrival at the PACU and across 4 measurement times during the initial POD was evaluated by a linear mixed effects model with autoregressive covariance matrix.

The licorice and sugar-water groups were compared on the incidence of coughing over the 5 measurement times (i.e., immediately after extubation, 0.5 and 1.5 hours after arrival in the PACU, 4 hours after surgery, and on the first POD morning) with use of the modified Mantel-Haenszel test[1] adjusting for the within-patient correction. Furthermore, we evaluated the overall treatment effect on amount of coughing by a multivariate (i.e., multiple outcome) generalized estimating equation (GEE) with cumulative logit link, which gives the estimated odds ratio of rating a lower (better) coughing score after adjusting for within-patient correlation exhibited among the 5 assessments.

Sample Size Consideration

We expected the incidence of postoperative sore throat at 30 minutes, 1.5 hours, and 4 hours to be approximately 0.70, 0.70, and 0.55, respectively, in our control group, based on Agarwal et al.[14] We designed the study to have a 90% power at the 0.05 overall significance level for detecting a relative 30% reduction across the time points in the licorice versus placebo groups. We assumed an autoregressive correlation structure with adjacent pairwise correlation of 0.50. Assuming no interaction between group and time, but differential treatment effects across conditions, a maximum sample size of $N = 236$ was needed, adjusting for 2 interim analyses and a final analysis.

All results are reported with an interim-adjusted confidence interval (CI), estimated using the Z-statistic efficacy criterion of 2.284 (i.e., corresponding to an α of 0.0224). For each repeat measures outcome, the treatment effect at each specific time was reported for descriptive purposes, regardless of the significance of the corresponding treatment-by-time interaction, using χ^2 test, student t test, or a multivariate GEE model, as appropriate. The corresponding CI was further adjusted for multiple comparisons by Bonferroni correction, using the Z-statistic criteria of 2.675, 2.770, and 2.842 for the outcomes with 3, 4, and 5 measurement times,

respectively. All tests were 2-tailed. The significance level for each hypothesis was 0.05 for the main effect and 0.10 for the treatment-by-time interaction, if applicable.

Sample size calculations were based on work by Dahmen et al.[21] and their GEEsize macro, as well as East software by Cytel Inc. (Cambridge, MA). SAS software version 9.2.2 for Windows (SAS Institute, Cary, NC), R software version 2.12.0. for Windows (The R Foundation for Statistical Computing, Vienna, Austria), and East 5 software (Cytel Inc.) were used for analyses.

RESULTS

Two hundred thirty-six patients (118 patients in each group) were included in this study. One patient, assigned to the sugar-water group, was withdrawn due to surgery schedule changes (emergency surgery) and was not included in the analysis (Fig. 1). In addition, 2 patients (1 patient in each group) did not have any outcome assessments, because they were still intubated at the assessment times. These 2 patients were included in the analysis using a conservative intention-to-treat basis; we assigned the observed worst and best outcomes to the patient in the licorice group and in the sugar-water group, respectively. Progression of the interim analyses toward efficacy and futility is shown in Figure 2.

The licorice and the sugar-water groups were well balanced (absolute value of STD ≤0.2) on demographics and baseline characteristics (Table 1). We thus did not adjust for any baseline variables when comparing the licorice gargle users and the sugar-water gargle users on the outcomes.

Primary Analysis

The observed incidences of postoperative sore throat at rest in the licorice and the sugar-water groups were 19% and 36% at 0.5 hours after arrival in the PACU, 10% and 35% at 1.5 hours after arrival, and 21% and 45% at 4 hours after surgery, respectively (Table 2).

The estimated treatment effects (relative risk [RR]) of licorice versus sugar-water on reducing the incidence of sore throat at rest were 0.54 (95% CI, 0.30–0.99), 0.31 (0.14–0.68), and 0.48 (0.28–0.83), at 0.5 and 1.5 hours after arrival in the PACU and 4 hours after surgery, respectively (Table 2). Although the above estimated treatment effect varied from 0.31 to 0.54 (treatment-by-time interaction: $P = 0.02$), preoperative gargling with licorice significantly reduced the incidence of sore throat at all 3 measurement times. The overall RR of experiencing sore throat across the 3 measurements during the first 4 hours after surgery was estimated as 0.46 (95% CI, 0.29–0.72, licorice versus sugar-water; $P < 0.001$), as analyzed with repeated-measures analysis of variance.

Secondary Analyses

Preoperative gargling with licorice significantly reduced sore throat pain during the first initial POD ($P < 0.001$); the overall mean reduction in the pain score was estimated as 0.55 on a 0 to 10 scale (95% CI, 0.27–0.84; Table 3). The treatment effect of licorice on sore throat pain score was consistent between the 2 conditions (i.e., at rest and during swallowing) at 30 minutes after arrival at the PACU (treatment-by-condition interaction: $P = 0.11$) and across 4

Figure 1. Trial diagram.
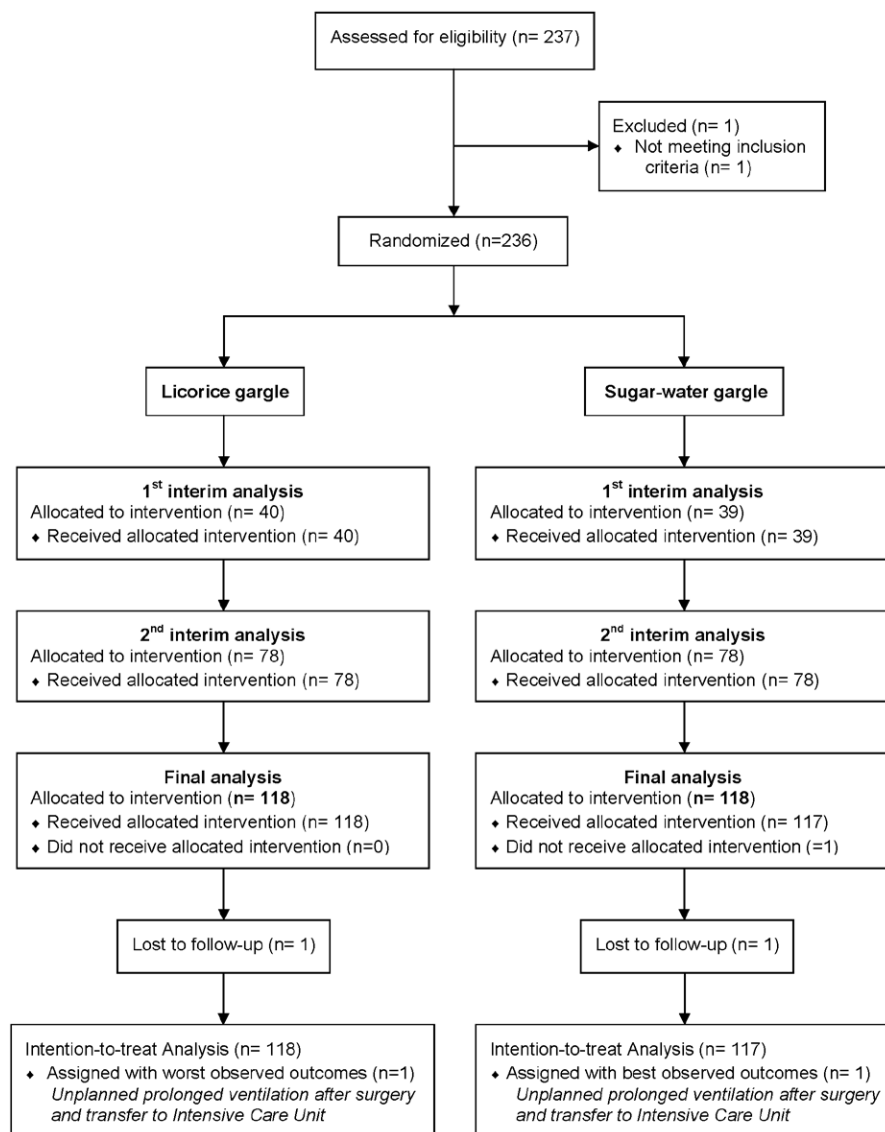
measurement times during the initial POD (treatment-by-time interaction: $P = 0.15$).

Compared with sugar-water, preoperative gargling with licorice significantly reduced the incidence of sore throat during swallowing at 0.5 hours after arrival in the PACU (RR [95% CI]: 0.53 [0.32–0.88], $P = 0.003$); and the incidence of sore throat at rest on the first POD morning: 0.54 [0.33–0.87], $P = 0.003$.

Preoperative gargling with licorice significantly reduced the incidence of coughing across all 5 assessment times (i.e., immediately after extubation, 0.5 and 1.5 hours after arrival in PACU, 4 hours after surgery, and on the first POD morning) as compared with sugar-water ($P = 0.01$, Table 3). The estimated overall RR during the first initial POD was 0.68 (95% CI, 0.48–0.96, licorice versus sugar-water, Table 3). No treatment-by-time interaction was observed for the incidence of coughing ($P = 0.94$).

Patients in the licorice group were 1.7 times (95% CI, 1.1–2.7) more likely to rate a lower (better) coughing score during the first POD as compared with patients in the sugar-water group ($P < 0.001$, Table 3). The effect of licorice on

amount of coughing did not vary over the 5 measurements (treatment-by-time interaction: $P = 0.91$). Severe coughing was only reported by 2 patients, 1 in each group, on the first POD morning. No side effects related to the use of licorice, including allergic reactions, discomfort, or mucosal burning were observed.

DISCUSSION

Postextubation coughing and sore throat are minor but common postoperative complaints. In general, our patients reported only mild sore throat which is in distinct contrast to previous reports.[7,22–24] Low pain scores in our study may have resulted from the fact that our intubating anesthesiologists were highly experienced and thus unlikely to produce tissue trauma. Furthermore, analgesics, including paracetamol and opioids, given for the surgical incision will of course provide analgesia in the throat. However, the incidence of sore throat is variously reported to range from 14% to 90%,[7,22–24] with the incidence of hoarseness ranging from 10% to 50%.[22,24,25] This wide range may have been due to variations in the skill and experience levels of the
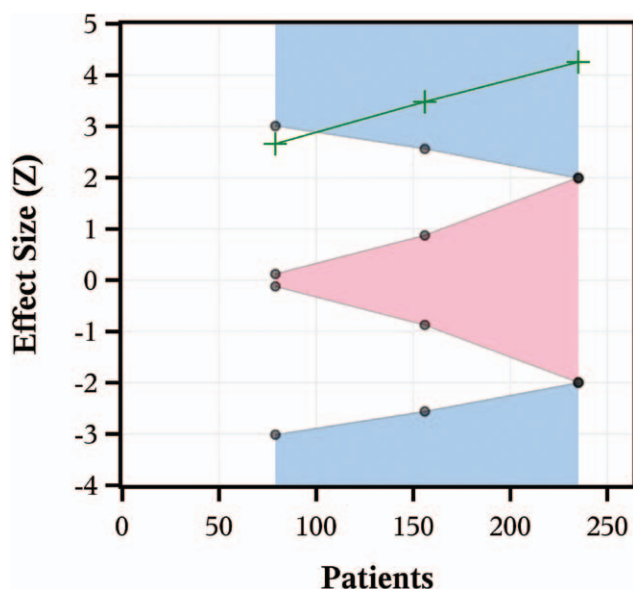
Figure 2. Plot of standardized effect size Z for 2 interim analyses (at N = 79 and N = 179) and the final analysis (at N = 235), which are shown by the solid line (+) with Z-statistics of 2.66, 3.48, and 4.25, respectively. The 3 regions from top to bottom correspond to efficacy, futility, and harm, respectively. At the second interim analysis, the study crossed the efficacy boundary. However, the study executive committee decided to continue the study to obtain a more precise estimate of the treatment effect and because there was little if any risk to participants.

performing physician, atraumatic extubation, along with predisposing factors including: patient sex, cuff design, excessive cuff pressure from nitrous oxide, use of succinylcholine, type of surgery, preexisting tracheal disease, and

Table 1. Demographics and Baseline Characteristics (N = 235)

Variable	Licorice (N = 118)	Sugar-water (N = 117)	Standardized difference[a]
Age, y	57 ± 15	58 ± 16	−0.09
Gender (female), %	42	38	0.08
Body mass index, kg/m²	26 ± 4	26 ± 4	−0.01
Smoking, %			−0.01
Current	38	38	
Past	31	31	
Never	31	31	
Pain (yes), %	0	2	−0.19
ASA physical status, %			−0.07
I	19	16	
II	57	57	
III	25	26	
Mallampati score, %			−0.20
1	33	26	
2	56	59	
3	8	14	
4	0	1	
Surgery size, %			−0.17
Small[b]	27	21	
Medium[b]	64	71	
Large[b]	9	9	

Summary statistics presented as percent of patients or mean ± SD.

[a]Standardized difference (licorice − sugar-water) defined as the difference in means or proportions divided by the pooled standard deviation; >0.2 in absolute value indicates imbalance.

[b]Surgery size: small (thoracoscopy); medium (thoracotomy <3 h), large (thoracotomy >3 h or blood loss >1000 mL).

prolonged laryngoscopy.[13,26] Extensive damage to the laryngeal and tracheal epithelia occurs as a result of tracheal intubation, even when intubation lasts as little as an hour and intubation is uneventful.[27] An important factor appears to be endotracheal tube size.[27–29] We therefore studied patients having thoracic surgery who required intubation with double-lumen tubes which have a much larger diameter than conventional single-lumen tubes.

Our primary result is that preoperative gargling with licorice significantly reduces the incidence of early postoperative sore throat compared with gargling sugar solution in patients intubated with double-lumen tubes. The overall treatment effect was a factor-of-2 reduction in sore throats: RR 0.46 (95% CI, 0.29–0.77; P < 0.001). Furthermore, benefit was sustained during coughing and over time. That such a simple, inexpensive, and low-risk prophylactic intervention so effectively prevents a common and annoying complication of intubation is remarkable, and seems well worth implementing into routine clinical practice.

Small studies reporting large treatment effects are often subsequently proven wrong or have substantially overestimated actual benefit.[30] However, our results in 235 patients were nearly identical to the only previous publication that enrolled just 40 patients.[14] All available data thus strongly support the conclusion that just a 1-minute preoperative gargle with licorice solution halves the risk of postoperative sore throats.

While preoperative gargling with licorice might seem unlikely to reduce the risk of postoperative sore throat, we note that others have demonstrated benefit with ketamine,[31,32] azunol,[8] and strepsils.[13,33] Corticosteroids also appear helpful,[34] and many investigators have evaluated the use of inhaled or topical steroids.[35] For example, Park et al.[36] showed that applying triamcinolone acetonide paste to the endotracheal tube reduces the incidence of sore throat compared with the application of chlorhexidine jelly. Spraying the endotracheal tube with benzydamine hydrochloride, a nonsteroidal anti-inflammatory drug, also reduces the incidence of sore throat.[10]

Unlike many airway studies that evaluated patients having minor procedures, most of our patients had thoracotomies, which are among the most painful operations. Furthermore, our patients were given opioids which simultaneously diminishes the intensity of all pain, including sore throat pain. It is thus unsurprising that they rated sore throat pain as being of modest intensity. But even pain of modest intensity contributes to overall patient discomfort and deserves consideration.

The sweetness of each gargling solutions used in this study was considered subjectively equal by an independent pharmacist. Nevertheless, based on its distinctive taste, patients could potentially tell which was licorice. However, patients were told that 2 different solutions for prevention of postextubation sore throat were used, but were not told what flavors were being tested. It is thus unlikely that their knowledge of being given licorice would provide any substantial placebo effect over the control sugar gargle. Furthermore, all outcomes were evaluated by independent and blinded investigators.

In summary, licorice gargling halved the incidence of sore throat over the first POD. Preinduction gargling with

Table 2. Primary Results—Treatment Effect of Preoperative Gargling with Licorice on Incidence of Sore Throat at Rest Through the First 4 Postextubation Hours

Sore throat at rest[a]	Licorice (N = 117)[b] No. (%)	Sugar-water (N = 116)[b] No. (%)	Relative risk[c] (95% CI)[d] (licorice versus sugar)	P[e]
			Overall: 0.46 (0.29–0.72)	**<0.001**[f]
0.5 h	22 (19)	42 (36)	0.54 (0.30–0.99)	**0.005**
1.5 h	12 (10)	41 (35)	0.31 (0.14–0.68)	**<0.001**
4 h	24 (21)	52 (45)	0.48 (0.28–0.83)	**<0.001**

CI = confidence interval.

[a]0.5 and 1.5 h after arrival in the postanesthesia care unit; and 4 h after surgery.

[b]Sore throat assessments for 2 patients (i.e., 1 in each group) were not done, because they were still intubated at the assessment times. Data are presented as numbers (percentage).

[c]The analysis was on the conservative intention-to-treat basis, by assuming the patient without sore throat assessments in the licorice group experienced sore throat at every assessment, and assuming the patient in the sugar-water group did not experience sore throat, respectively.

[d]In addition to the adjustment for the interim analyses, the confidence intervals for the treatment effect at individual times were further adjusted for multiple comparisons using Bonferroni correction. The Z-statistic criterion was 2.284 for the overall treatment effect adjusting for the interim analysis, and 2.675 for the treatment effect at individual times.

[e]χ^2 test (the significance criterion was 0.0224/3 = 0.0075, Bonferroni correction), unless specified. P values in bold are significant.

[f]Modified Mentel-Haenszel test[1] (significance criterion: 0.0224).

Table 3. Secondary Results—Treatment Effects of Preoperative Gargling Licorice on Secondary Outcomes

Secondary outcome	Licorice (N = 117)[a]	Sugar-water (N = 116)[a]	Treatment effect[b] (95% CI)[c] (licorice versus sugar)	P[d]
			Relative risk	
Sore throat swallowing (0.5 h), yes (number of subjects)	22	43	0.53 (0.32 to 0.88)	**0.003**
Sore throat at rest (POD 1 morning), yes (number of subjects)	24	46	0.54 (0.33 to 0.87)	**0.003**
			Mean difference	
Sore throat score,[e] 0–10: no to worst pain			Overall: −0.55 (−0.84 to −0.27)	**<0.001**[f]
0.5 h (at rest)	0.27 ± 0.68	1.03 ± 1.55	−0.70 (−1.16 to −0.23)	**<0.001**[g]
0.5 h (swallowing)	0.35 ± 0.76	0.91 ± 1.38	−0.98 (−1.65 to −0.30)	**<0.001**[g]
1.5 h (at rest)	0.27 ± 0.68	1.03 ± 1.55	−0.63 (−1.02 to −0.24)	**<0.001**[g]
4 h (at rest)	0.35 ± 0.76	0.91 ± 1.38	−0.50 (−0.94 to −0.06)	**<0.001**[g]
POD 1 morning (at rest)	0.14 ± 0.45	0.82 ± 1.32	−0.28 (−0.62 to 0.07)	0.03[g]
			Relative risk	
Coughing, yes (no. of subjects)			Overall: 0.68 (0.48 to 0.96)	0.01[h]
Immediately after extubation	29	45	0.66 (0.38 to 1.15)	0.03
30 min	18	28	0.67 (0.32 to 1.44)	0.13
1.5 h	16	25	0.67 (0.30 to 1.52)	0.16
4 h	28	39	0.74 (0.41 to 1.33)	0.14
POD 1 morning	31	48	0.66 (0.39 to 1.13)	0.02
			Odds ratio[i]	
Amount of coughing, no/mild/moderate/severe (no. of subjects)			Overall: 1.70 (1.08 to 2.69)	**<0.001**[j]
Immediately after extubation	88/25/4/0	71/30/15/0	2.02 (0.90 to 4.55)	0.01[j]
30 min	99/18/0/0	88/24/4/0	1.66 (0.65 to 4.25)	0.12[j]
1.5 h	101/16/0/0	91/23/2/0	1.61 (0.61 to 4.27)	0.17[j]
4 h	89/26/2/0	77/35/4/0	1.51 (0.67 to 3.41)	0.15[j]
POD 1 morning	86/27/3/1	68/42/5/1	1.80 (0.82 to 3.94)	0.03[j]

0.5 and 1.5 h after arrival in postanesthesia care unit; 4 h after surgery; and POD 1 morning.

CI = confidence interval; POD = postoperative day.

[a]Assessments for 1 patient in each group were not done, because they were still intubated at the assessment times.

[b]The analyses were on the conservative intention-to-treat basis, by assigning the patient without outcome assessments in the licorice group with the observed worst outcomes, and assigning the patient in the sugar-water group with the best observed outcomes, respectively.

[c]In addition to adjustment for the interim analyses, the confidence intervals for the treatment effect at individual times were further adjusted for multiple comparisons using Bonferroni correction. The Z-statistic criterion was 2.284 for the overall treatment effect, and 2.842 for the treatment effect at individual times for outcomes with 5 measurements.

[d]χ^2 test (the significance criteria were 0.0224 for sore throat at rest at POD 1 and for sore throat during swallowing at 0.5 h, and 0.0224/5 = 0.0045 for incidence of coughing, Bonferroni correction), unless specified. P values in bold are significant.

[e]Although visual analog scale sore throat score was not normally distributed, the residuals from the mixed effect model were approximately normally distributed. There were several outliers, however none of them was influential based on cook's distance (all <0.005) and difference of fits statistics (all <0.1). Furthermore, nonparametric Wilcoxon test provides consistent conclusions (P-value = 0.0005, 0.0004, <0.0001, 0.0002, and 0.003 for assessment at 30 min at rest, during swallowing, 1.5, 4 h, and POD 1, respectively).

[f]Mixed linear model with Autoregressive covariance matrix (significance criterion: 0.0224).

[g]Student t test (significance criterion: 0.0045).

[h]Modified Mentel-Haenszel test[20] (significance criterion: 0.0224).

[i]Odds ratio of rating a lower (better) score.

[j]Multivariate generalized estimating equation model with cumulative logit link (significance criterion was 0.024 for the overall and 0.0045 for each individual measurement).

licorice appears to be a simple way to prevent a frequent and unpleasant postoperative complication. ⬚

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