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REPORTS OF ORIGINAL INVESTIGATIONS

Effect of prophylactic benzydamine hydrochloride on postoperative sore throat and hoarseness after tracheal intubation using a double-lumen endobronchial tube: a randomized controlled trial

L'effet d'une prophylaxie de chlorhydrate de benzydamine sur les maux de gorge et l'enrouement postopératoires après une intubation trachéale à l'aide d'une sonde endobronchique à double lumière: une étude randomisée contrôlée

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Abstract

Purpose *We evaluated the prophylactic effect of benzydamine hydrochloride (BH) spray on postoperative sore throat and hoarseness secondary to intubation with a double-lumen endobronchial tube (DLT).*

Methods *Ninety-two adult patients undergoing thoracic surgery using DLT intubation were studied. The DLT cuff and oropharyngeal cavity were sprayed with normal saline (Group S; n = 46) or BH (Group BH; n = 46) prior to intubation. Postoperative sore throat and hoarseness were evaluated at one, six, and 24 hr after surgery. Sore throat was evaluated using a 0-100 mm visual analogue scale (VAS). Hoarseness was defined as a change in voice quality.*

Results *Compared with Group S, postoperative sore throat occurred less frequently in Group BH at one hour (mean difference, 28.3%; 95% confidence interval [CI], 8.7 to 45.1; P = 0.01), at six hours (mean difference, 32.6%; 95% CI, 12.6 to 49.2; P < 0.01), and at 24 hr (mean difference, 28.3%; 95% CI, 9.3 to 44.7; P = 0.01) after surgery. Group BH had lower VAS scores for postoperative sore throat at one hour (mean difference, 12.8; 95% CI, 4.9 to 20.7), at six hours (mean difference, 11.9; 95% CI, 4.8 to 19.1; P < 0.01), and at 24 hr (mean difference, 5.3; 95% CI, 0.9 to 9.7; P = 0.01) after surgery. Hoarseness also occurred less frequently in Group BH at one hour (mean difference, 23.9%; 95% CI, 6.8 to 39.6; P = 0.01), at six hours (mean difference, 23.9%; 95% CI, 7.4 to 39.3; P = 0.01), and at 24 hr (mean difference, 21.7%; 95% CI, 5.5 to 37.0; P = 0.02) after surgery (P < 0.01).*

Conclusions *Prophylactic application of BH to the DLT cuff and oropharyngeal cavity reduces the incidence and severity of postoperative sore throat and the incidence of hoarseness associated with DLT intubation. The trial was registered at the Clinical Research Information Service (KCT0001068).*

Résumé

Objectif *Nous avons évalué l'effet prophylactique d'un vaporisateur de chlorhydrate de benzydamine (CB) sur les*

Author contributions *Jee-Eun Chang, Seong-Won Min, Chong-Soo Kim,* and *Jin-Young Hwang* helped design the study. *Jee-Eun Chang, Sung-Hee Han, Yong-Suk Kwon,* and *Jin-Young Hwang* helped conduct the study. *Jee-Eun Chang, Seong-Won Min, Chong-Soo Kim,* and *Jin-Young Hwang* helped analyze the data. *Jee-Eun Chang* and *Jin-Young Hwang* helped write the manuscript. *Jee-Eun Chang* is the author responsible for archiving the study files. All authors have seen the original study data and reviewed the analysis of the data.

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maux de gorge et l'enrouement postopératoires découlant d'une intubation réalisée avec une sonde endobronchique à double lumière (SDL).

Méthode *Quatre-vingt-douze patients adultes subissant une chirurgie thoracique et intubés avec une SDL ont pris part à l'étude. Le ballonnet de la SDL et la cavité oropharyngée ont été vaporisés avec du sérum physiologique (groupe S; n = 46) ou du CB (groupe CB; n = 46) avant l'intubation. Les maux de gorge et l'enrouement postopératoires ont été évalués à une, six et 24 heures après la chirurgie. Les maux de gorge ont été évalués à l'aide d'une échelle visuelle analogique (EVA) de 0-100 mm. L'enrouement a été défini comme un changement de la qualité vocale.*

Résultats *Par rapport au groupe S, les maux de gorge postopératoires étaient moins fréquents dans le groupe CB une heure (différence moyenne, 28,3 %; intervalle de confiance [IC] 95 %, 8,7 à 45,1; P = 0,01), six heures (différence moyenne, 32,6 %; IC 95 %, 12,6 à 49,2; P < 0,01) et 24 heures (différence moyenne, 28,3 %; IC 95 %, 9,3 à 44,7; P = 0,01) après la chirurgie. Les scores du groupe CB sur l'EVA étaient plus bas en matière de maux de gorge postopératoires une heure (différence moyenne, 12,8; IC 95 %, 4,9 à 20,7), six heures (différence moyenne, 11,9; IC 95 %, 4,8 à 19,1; P < 0,01) et 24 heures (différence moyenne, 5,3; IC 95 %, 0,9 à 9,7; P = 0,01) après la chirurgie. L'enrouement était également moins fréquent dans le groupe CB une heure (différence moyenne, 23,9 %; IC 95 %, 6,8 à 39,6; P = 0,01), six heures (différence moyenne, 23,9 %; IC 95 %, 7,4 à 39,3; P < 0,01) et 24 heures (différence moyenne, 21,7 %; IC 95 %, 5,5 à 37,0; P = 0,02) après la chirurgie (P < 0,01).*

Conclusion *L'application prophylactique de CB au ballonnet de la SDL et à la cavité oropharyngée réduit l'incidence et la gravité des maux de gorge postopératoires et l'incidence d'enrouement associées à l'intubation via SDL. Cette étude a été enregistrée au Clinical Research Information Service (KCT0001068).*

Postoperative sore throat and hoarseness are common following tracheal intubation, with an incidence of 14.4-73.9%.[1-3] These adverse events, which are closely related to endotracheal tube (ETT) size,[2] may have a negative effect on patients' satisfaction and activities after surgery.[4] The double-lumen endobronchial tube (DLT) used for one-lung ventilation is more likely to cause a higher incidence of postoperative hoarseness than a bronchial blocker inserted via a standard tracheal tube.[5] Moreover, although silicone DLTs are associated with a lower incidence of sore throat than polyvinyl chloride DLTs,[6] the latter are used routinely in the clinical setting.

The prophylactic use of dexamethasone has been reported to reduce the incidence and severity of postoperative sore throat and hoarseness associated with DLT intubation[7]; however, the potential side effects of steroids limit their use. Whereas inflation of the ETT cuff with lidocaine has been reported to alleviate postoperative sore throat,[8] application of lidocaine to the oropharyngeal cavity or laryngotracheal area seems to be ineffective.[9,10] Ketamine gargle has been suggested to reduce postoperative sore throat, but the systemic effect of ketamine may be of consequence.[3]

Benzydamine hydrochloride (BH), a topical nonsteroidal anti-inflammatory drug (NSAID) with analgesic properties, has been reported to reduce the incidence and severity of postoperative sore throat when administered as an oral gargle or spray on the ETT cuff or oropharyngeal cavity.[11,12] As such, we evaluated whether applying BH to the ETT cuff and oropharyngeal cavity would reduce postoperative sore throat and hoarseness in patients with DLT tracheal intubation.

Methods

This study was approved by the Ethics Committee of our hospital (no. 20131120/16-2013-163/121) and written informed consent was obtained from all patients.

Adult patients undergoing thoracic surgery requiring DLT endotracheal intubation for one-lung ventilation were enrolled in the study. Patients were excluded if they had a sore throat, hoarseness, coagulopathy, a known or predicted difficult airway, or allergy to acetylsalicylic acid or NSAIDs. Patients classified as Cormack-Lehane view 3 or 4[13] during laryngoscopy and those who required postoperative mechanical ventilation were also excluded.

Patients were randomly allocated to the saline treatment group (Group S) or the BH treatment group (Group BH) using a computer-generated program, Random Allocation Software, version 1.0 (Isfahan University of Medical Sciences, Isfahan, Iran) with a block size of four and a 1:1 allocation ratio. The randomization sequence was kept in consecutively numbered opaque sealed envelopes. Colleagues not involved in the study determined the treatment allocation by opening each envelope in sequence and preparing a BH or saline solution identical in appearance and labelled with the patients' identification number.

No premedication was administered to the patients. Intraoperative monitoring included electrocardiogram, pulse oximetry, gas analyzer, and noninvasive and invasive arterial pressure. Anesthesia was induced using propofol 1.5 $mg \cdot kg^{-1}$ and fentanyl 1.5-2.0 $\mu g \cdot kg^{-1}$, and rocuronium 0.6 $mg \cdot kg^{-1}$ was administered to achieve

neuromuscular blockade. Before intubation, the DLT endotracheal cuff and oropharyngeal cavity were each sprayed with three puffs of normal saline (Group S) or 0.3% BH (total 0.9 mg, Difflam^{TM}; iNova Pharmaceuticals Pty Ltd., Australia). Saline or BH were applied in the oropharyngeal cavity close to the vocal cords. Application of the study drugs was performed under direct laryngoscopy by an anesthesiologist blinded to the treatment. Tracheal intubation was subsequently performed using a Broncho-Cath^{TM} DLT (Mallinckrodt Medical Inc., Athlone, Ireland), size 37 Fr for males and size 35 Fr for females. Anesthesia was maintained with sevoflurane 2-4% end-tidal concentration in an air/oxygen mixture with intermittent fentanyl and rocuronium administered as required. Immediately following intubation and repositioning, fibreoptic bronchoscopy was used to confirm correct placement of the DLT. Intracuff pressure was monitored with a VBM handheld aneroid manometer (Sulz, Germany) every 30 min and maintained at 20 cm H_2O.

At the end of the operation, a patient-controlled analgesia (PCA) device was connected to the intravenous line and programmed to deliver fentanyl 10-20 $\mu g \cdot mL^{-1}$ and ketorolac 1.5-3.0 $mg \cdot mL^{-1}$ at a continuous infusion rate of 1 $mL \cdot hr^{-1}$ with a bolus dose of 1 mL (15 min lockout time). Residual neuromuscular block was reversed at the end of the procedure by pyridostigmine and glycopyrrolate. When patients were fully recovered and able to obey commands, tracheal extubation was carefully performed after gentle suctioning of oral secretions.

During tracheal intubation, we recorded the Cormack-Lehane view, resistance to DLT insertion (none, mild, moderate), number of intubation attempts, and time to achieve intubation. We also recorded the time for positioning the DLT, the number of repositionings, the duration of one-lung ventilation and tracheal intubation, and the total amount of fentanyl administered.

Postoperative sore throat and hoarseness were evaluated at one, six, and 24 hr after tracheal extubation by an observer blinded to the treatments. Sore throat was evaluated using a 0-100 mm visual analogue scale (VAS), 0 = no pain to 100 = worst pain imaginable. The incidence of sore throat was scored as 'No' with a VAS of 0 or 'Yes' with all other VAS values. Hoarseness was defined as a change in voice quality assessed by patients. If patients had a voice quality change during the observation period, the incidence of hoarseness was scored as 'Yes'.

The side effects of benzydamine hydrochloride (including numbness, stinging or burning sensation, cough, dry mouth, and nausea and vomiting), medications given for postoperative analgesia, and PCA drug consumption were recorded.

The primary aim of the present study was to compare the two groups with respect to the incidence of postoperative sore throat. Based on the results of a preliminary study in which the incidence of sore throat following DLT intubation was approximately 59%, 44 patients were required for each group to detect a 50% reduction in the incidence of postoperative sore throat ($\alpha = 0.05$, $\beta = 0.20$). Thus, 49 patients per group were enrolled to compensate for possible dropouts. We used SPSS® version 20 (IBM Inc., Armonk, NY, USA) to conduct the statistical tests. The categorical and continuous data are expressed as frequencies (%) and mean (SD), respectively. Point and interval estimates were determined for between-group differences. The occurrence of sore throat and hoarseness, the number of intubation attempts and DLT repositioning, and the resistance to DLT insertion were compared using Fisher's exact test. The intensity of postoperative sore throat, the time to achieve tracheal intubation and DLT positioning, and the duration of one-lung ventilation and tracheal intubation were assessed using the Mann–Whitney U test. All reported *P* values are two-sided.

Results

Ninety-eight patients were recruited from December 2013 to October 2014. Three patients did not meet the inclusion criteria, and the remaining 95 patients were randomized into the two groups. Two patients, one in each group, were classified as Cormack-Lehane view 3 during laryngoscopy and were excluded, and one patient in Group S was excluded because of delayed tracheal extubation. Thus, 92 patients were included in the analysis (Fig. 1).

Table 1 shows patient characteristics, postoperative PCA use, total fentanyl administration during the surgery and within 24 hr after surgery, type of surgery, surgery duration, and duration of anesthetic. No patient received dexamethasone during the perioperative period. Six patients in Group S and five patients in Group BH received ketorolac tromethamine 30 mg for analgesia within 24 hr after surgery as rescue analgesia. The Cormack-Lehane view, number of intubation attempts, resistance to DLT insertion, time for tracheal intubation and DLT positioning, number of repositionings, and the duration of one-lung ventilation and tracheal intubation were similar between the two groups (Table 2).

The incidence of postoperative sore throat and hoarseness is shown in Table 3. In Group BH, 10/46 (21.7%) patients experienced postoperative sore throat at one hour after surgery compared with 23/46 (50.0%) patients in Group S (mean difference, 28.3%; 95% confidence interval [CI], 8.7 to 45.1; relative risk reduction, 56.5%; 95% CI, 19.2 to 76.6; $P = 0.01$). Following surgery, the incidence of postoperative sore

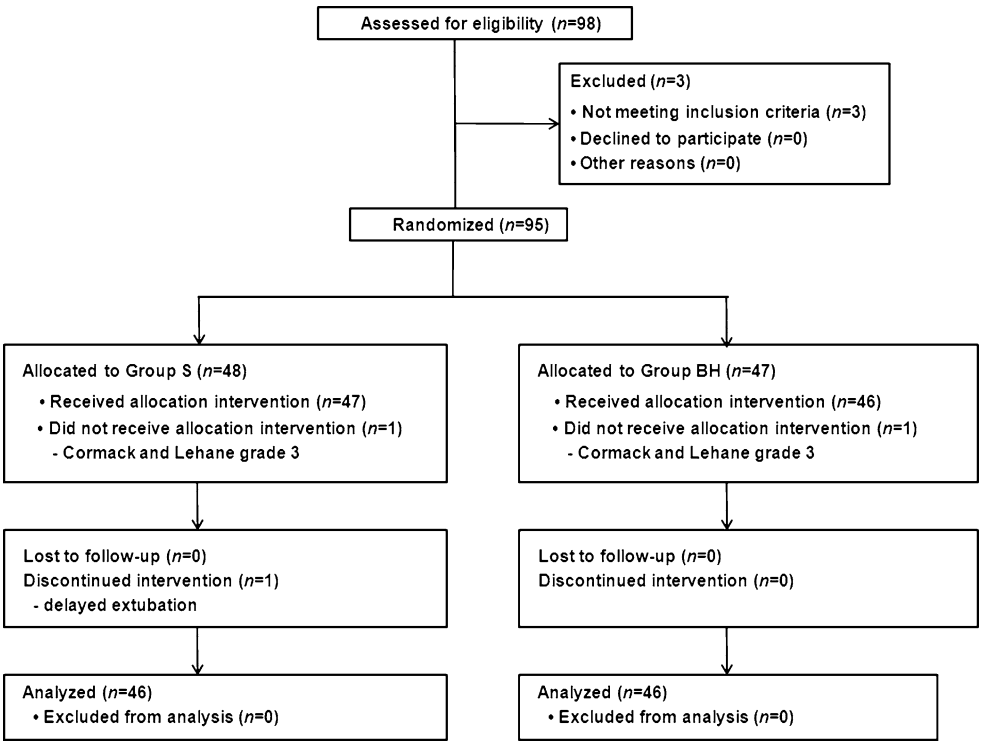

Fig. 1 Flow diagram. Three of the 98 patients assessed for eligibility were excluded. Of the remaining 95 patients, three were excluded owing to a Cormack-Lehane grade 3 view (n = 2) or delayed tracheal extubation (n = 1). There were 92 patients included in the analysis. Group S = saline treatment group; Group BH = benzydamine hydrochloride treatment group

throat was significantly lower in Group BH than in Group S at six hours (23.9% *vs* 56.5%, respectively; mean difference, 32.6%; 95% CI, 12.6 to 49.2; relative risk reduction, 57.7%; 95% CI, 24.9 to 76.2; $P < 0.01$) and at 24 hr (17.4% *vs* 45.7%, respectively; mean difference, 28.3%; 95% CI, 9.3 to 44.7; relative risk reduction, 61.9%; 95% CI, 23.0 to 81.2; $P = 0.01$). Furthermore, the incidence of hoarseness after surgery was lower in Group BH than in Group S at one hour (10.9% *vs* 34.8%, respectively; mean difference, 23.9%; 95% CI, 6.8 to 39.6; relative risk reduction, 68.8%; 95% CI. 21.8 to 87.5; $P = 0.01$), at six hours (8.7% *vs* 32.6%, respectively; mean difference, 23.9%; 95% CI, 7.4 to 39.3; relative risk reduction, 73.3%; 95% CI, 25.7 to 90.4; $P = 0.01$), and at 24 hr (8.7% *vs* 30.4%, respectively; mean difference, 21.7%; 95% CI, 5.5 to 37.0; relative risk reduction, 71.4%; 95% CI, 19.7 to 89.8; $P = 0.02$). Following surgery, the mean (SD) VAS score for the severity of sore throat was significantly lower in Group BH than in Group S at one hour [7.2 (14.6) *vs* 20.0 (22.7), respectively; mean difference, 12.8; 95% CI, 4.9 to 20.7; $P < 0.01$], at six hours [5.9 (12.6) *vs* 17.8 (20.9), respectively; mean difference, 11.9; 95% CI, 4.8 to 19.1; $P < 0.01$], and at 24 hr [3.0 (8.4) *vs* 8.3 (12.5), respectively; mean difference, 5.3; 95% CI, 0.9 to 9.7; $P = 0.01$] (Fig. 2).

None of the patients complained of cough, numbness, or a stinging or burning sensation. Three patients in each group experienced dry mouth. The incidence of nausea and vomiting was similar between the two groups (Group S *vs* Group BH, 15.2% *vs* 10.9%, respectively; mean difference, 4.3%; 95% CI, −10.0 to 18.7; $P = 0.76$).

Discussion

Our findings indicate that the prophylactic application of BH to the DLT cuff and oropharyngeal cavity reduced the incidence and severity of postoperative sore throat and the incidence of hoarseness at one, six, and 24 hr after tracheal intubation using a DLT.

Double-lumen endobronchial tubes are commonly used for lung separation and one-lung ventilation and are associated with a higher rate of laryngeal complications, such as postoperative sore throat and hoarseness, compared with single-lumen ETTs.[5,14] The incidence of postoperative sore throat and hoarseness is directly correlated with the size of the ETT.[2,15] The outer diameter of a DLT (13-14 mm for sizes 37 and 39 Fr; 12-13 mm for size 35 Fr) is larger than that of a single-lumen tracheal tube (10.7 mm for 8.0-mm internal diameter [ID]; 10.0 mm for 7.5-mm ID; 9.5 mm for 7.0-mm ID). Moreover, DLTs typically require frequent manipulation and repositioning for optimal one-lung ventilation, resulting in friction between the DLT and airway that can cause airway injuries.[6] The preformed curve of the DLT may also contribute to laryngeal trauma during surgery and tracheal extubation.[5] The 45.7-56.5% incidence of postoperative sore throat in Group S during the first 24

Table 1 Patient characteristics

	Group S (n = 46)	Group BH (n = 46)
Age (yr)	56 (22-77)	55 (21-76)
Sex (M/F)	30/16	31/15
Height (cm)	165 (8)	167 (9)
Weight (kg)	60 (10)	62 (9)
Smoking history (Y/N)	17/29	15/31
PCA (Y/N)	42/4	44/2
Total fentanyl administration (μg)		
During the surgery	105 (18)	104 (16)
Within 24 hr after surgery	519(132)	513(158)
Surgery (VATS/Thoracotomy)	43/3	41/5
Operation time (min)	127 (92)	129 (102)
Anesthetic time (min)	174 (97)	177 (109)

Values are mean (range) for age, mean (SD), or patient numbers

Group BH = benzydamine hydrochloride treatment group; Group S = saline treatment group; PCA = patient-controlled analgesia; VATS = video-assisted thoracic surgery

Table 2 Factors related to tracheal intubation

	Group S (n = 46)	Group BH (n = 46)	Between-group difference	P value
Cormack-Lehane view (1/2)	37/9	36/10		1.00
Number of intubation attempts				0.36
1	42	40		
2	3	6		
3	1	0		
Resistance to DLT insertion				0.60
None	30	30		
Mild	15	16		
Moderate	1	0		
Time for tracheal intubation (sec)	27 (4.9)	26.1 (6.7)	1.2 (−1.2 to 3.6)	0.11
Time for DLT positioning (sec)	19.8 (7.5)	18.3 (7.1)	1.5 (−1.5 to 4.5)	0.56
Number of repositionings				0.97
0	27	31		
1	15	12		
2	3	2		
3	1	1		
Duration of one-lung ventilation (min)	115.6 (88.0)	113.0 (93.6)	2.6 (−35.0 to 40.2)	0.59
Duration of tracheal intubation (min)	164.8 (99.4)	164.2 (108.9)	0.6 (−42.6 to 43.8)	0.64

Values are mean (SD), patient numbers, or mean difference (95% confidence interval)

DLT = double-lumen endobronchial tube; Group S = saline treatment group; Group BH = benzydamine hydrochloride treatment group

hr after surgery is consistent with previous studies reporting an incidence of approximately 50% when no special precautions are taken to reduce this occurrence.[6,7]

Benzydamine hydrochloride, a topical NSAID with analgesic, antipyretic, and antimicrobial properties, can be applied topically and systemically to treat various types of inflammation. Benzydamine hydrochloride is absorbed rapidly and completely following systemic administration, whereas topical application results in slower, less complete absorption.[16] Thus, BH concentrations remain high in local tissue following topical application of the drug and may exert a therapeutic effect at the target site, limiting unnecessary systemic exposure. Topical administration of BH as an oral rinse has been shown to be an effective and safe treatment for pharyngitis[17,18] and radiation-induced oral mucositis in patients with head and neck tumours.[19,20]

Table 3 Incidence of postoperative sore throat and hoarseness

	Group S (n = 46)	Group BH (n = 46)	Between-group difference	P value
1 hr after surgery				
Sore throat	23 (50.0)	10 (21.7)	28.3% (8.7 to 45.1)	0.01
Hoarseness	16 (34.8)	5 (10.9)	23.9% (6.8 to 39.6)	0.01
6 hr after surgery				
Sore throat	26 (56.5)	11 (23.9)	32.6% (12.6 to 49.2)	< 0.01
Hoarseness	15 (32.6)	4 (8.7)	23.9% (7.4 to 39.3)	0.01
24 hr after surgery				
Sore throat	21 (45.7)	8 (17.4)	28.3% (9.3 to 44.7)	0.01
Hoarseness	14 (30.4)	4 (8.7)	21.7% (5.5 to 37.0)	0.02

Values are patient numbers (%) or between-group difference (95% confidence interval)

Group BH = benzydamine hydrochloride treatment group; Group S = saline treatment group

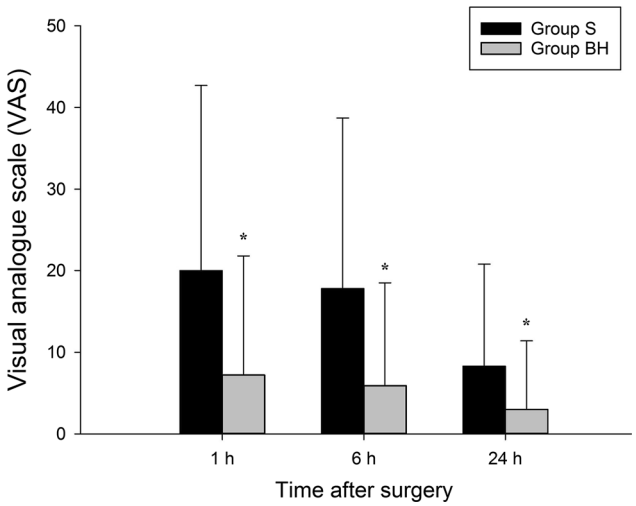

Fig. 2 Intensity of postoperative sore throat. Values are means (SD). Error bars indicate 1 SD. Group S = saline treatment group; Group BH = benzydamine hydrochloride treatment group. *$P < 0.05$ compared with Group S

Previous studies have shown that BH administered as either a prophylactic oral gargle or a spray on tracheal tube cuffs reduces the incidence and severity of postoperative sore throat.[11,12,21] Moreover, pre-emptive BH application to the pharynx has been found to decrease the incidence of sore throat following the use of a laryngeal mask[22] A postoperative flexible laryngoscopic assessment of vocal cord injuries revealed that the main injuries caused by DLT intubation are redness and edema at the vocal folds.[5] Thus, the anti-inflammatory and analgesic effect of BH can alleviate the sore throat and hoarseness caused by DLT intubation, particularly when it is applied to the DLT cuff and oropharyngeal cavity.

Potential adverse effects associated with the topical application of BH include local irritation, such as numbness and a burning or stinging sensation. Agarwal *et al.*[11] reported that two of 19 (10.5%) patients who gargled with a BH solution for 30 sec before the induction of anesthesia complained of numbness and dysgeusia. Furthermore, a previous study found that 8-10% of patients experienced local stinging or numbness of the throat and mouth when BH was topically applied to the oral mucosa before anesthesia induction.[12] Conversely, Mazzarella *et al.*[23] found that applying BH to the oropharyngeal cavity immediately before intubation and reapplying regularly for 48 hr after surgery produced a therapeutic effect without local or systemic side effects. Moreover, Huang *et al.*[12] reported that patients did not experience BH-related adverse effects when the drug was applied to the tracheal tube cuff. In our study, we hypothesize that BH sprayed over the DLT cuff and oropharyngeal cavity after induction of anesthesia decreased local irritation and so reduced complaints of BH-related adverse effects during the postoperative study period.

This study has several limitations. Although an equal dose of BH was administered to each patient, we cannot account for variable effect-site concentrations of the drug due to patient characteristics such as varied mucosal thickness in the oropharyngeal cavity or different volumes of saliva that may affect drug absorption.[24] Moreover, we did not evaluate coughing or bucking events during extubation that may have produced variable trauma and irritation. Postoperative BH administration (spray or gargle) combined with its prophylactic use as described may provide additional relief from postoperative sore throat and hoarseness. Further studies are required to evaluate the efficacy and safety of this strategy.

In conclusion, BH applied prophylactically to the DLT cuff and oropharyngeal cavity reduced the incidence and severity of postoperative sore throat and hoarseness at one, six, and 24 hr after surgery without adverse effects.

Declaration of interest The authors report no conflict of interest. We have no financial or other relationships that might lead to conflict of interests regarding this work. We alone are responsible for the content and writing of the paper.

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