Benzydamine Hydrochloride Spray for Reducing Postoperative Sore Throat after General Anesthesia with Laryngeal Mask Airway

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Objective: *To compare postoperative sore throat (POST) between patients receiving laryngeal mask airway (LMA) sprayed with either 0.3% benzydamine hydrochloride (BH) or normal saline.*

Material and Method: *This prospective, randomized, double-blind, controlled study was conducted in 80 patients scheduled for elective surgery under general anesthesia using LMA. They were randomly allocated to receive LMA sprayed with either 0.3% BH (Group BH) or normal saline (Group C). POST was evaluated at the first and forth postoperative hour. Dysphagia, dysphonia, local side effects of BH such as pharyngeal numbness or stinging sensation, and patient satisfaction were also recorded and analyzed.*

Results: *There were no significant differences in patient characteristics between the two groups. The incidences of patient without POST at the first and the forth postoperative hour in Group BH was higher than that in Group C (47.5% vs. 27.5%, p = 0.07 and 82.5% vs. 60.0%, p = 0.03, respectively). Patients in Group BH significantly had lower median severity of POST at the first and the forth postoperative hour. At the forth postoperative hour, there was a 22.5% (95% CI 3.3 to 41.7) absolute increase in the incidence of patients without POST in Group BH compared with Group C, and this was equal to a number needed to treat of 4.4 (95% CI 2.4 to 30.4). No serious airway complications or major adverse reactions were observed in either group. Patient satisfaction was significantly higher in Group BH.*

Conclusion: *BH sprayed on LMA cuff increased incidence of patients without POST, decreased POST severity, and increased patient satisfaction.*

Keywords: *Benzydamine hydrochloride, Laryngeal mask airway, Postoperative sore throat*

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Since the introduction of laryngeal mask airway (LMA) to the market in 1988, it has been used for general anesthesia all over the world. As a supraglottic airway device, LMA is considered to cause less airway trauma than endotracheal intubation. Nevertheless, the incidences of postoperative sore throat (POST) after LMA reported in literatures range between 5.8 and 34.0%[1,2]. The main etiology of POST is likely pharyngeal tissue trauma caused by the LMA cuff[2-4], which often occurs during insertion. Rieger et al demonstrated no correlation between LMA intracuff pressure and the incidences of POST[5]. Various medications to eliminate or minimize POST have been studied, including propofol[6], muscle relaxants[7], corticosteroids[8], and non-steroidal anti-inflammatory drugs (NSAIDs)[9].

Benzydamine hydrochloride spray (BH) is a topical NSAID that has local anesthetic and analgesic properties[10]. The major, but rare, side effect of BH is allergy. Minor side effects of BH include numbness, tingling, or abnormal sensation in the throat[1]. All of minor side effects normally resolve spontaneously. BH can be used both topically and systemically for treatment of active inflammation, but its local tissue concentration is higher after topical application[10]. It is, therefore, generally used for anti-inflammation in the mouth and throat for conditions that include pharyngitis, tonsillitis, and radiation-induced mucositis[11]. BH has been also proven to reduce POST after endotracheal intubation[12]. With the anti-inflammatory property and the proven efficacy of BH to reduce POST following endotracheal intubation,

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the investigators hypothesized that spraying BH on the LMA cuff would increase number of patients without POST after general anesthesia using LMA.

Material and Method

Patient population and study design

This prospective, randomized, double-blind controlled study was approved by the Institutional Review Board (Si 162/2014) and written informed consent was obtained from each participant. Patients scheduled for elective surgery under general anesthesia using LMA between June 2014 and December 2014 were enrolled in this study. Randomization was performed using randomization software and the allocation assignments were concealed in sealed envelopes.

Patients aged between 18 and 70 years old, American Society of Anesthesiologists (ASA) physical status I to III scheduled for general anesthesia using LMA were included. Patients with any of the following were excluded: allergy to BH or NSAIDs; high risk for gastrointestinal bleeding; severe liver or kidney disease, pregnant or breastfeeding women; full stomach; body mass index (BMI) $\geq$30 kg/m^2; operations involving oral cavity and/or neck; upper respiratory tract infection; upper airway abnormalities; pre-existing sorethroat; retained nasogastric or orogastric tube; or estimated duration of anesthesia <30 minutes. In order to investigate the efficacy of BH for decreasing the incidence and severity of POST, patients were randomly allocated to receive either 0.3% BH (Group BH) or normal saline (NSS) (Group C) sprayed on the LMA cuff prior to airway insertion. The LMA ProSeal™ Airway (Teleflex, Inc., Wayne, PA, USA) was the LMA used in this study. LMA size was selected on the basis of patient's body weight according to manufacturer's recommendation. The selected LMA was tested and prepared without addition of any other lubricant applied to the cuff. Four puffs of the study drug were sprayed onto the LMA cuff by one of the investigator. The LMA was inserted by anesthesia personnel with at least 6 months experience who was blinded to the study group after induction with propofol 1.5 to 2.5 mg/kg, fentanyl 1 to 2 mcg/kg or morphine 0.1 to 0.2 mg/kg, and atracurium 0.3 to 0.6 mg/kg or cisatracurium 0.1 to 0.15 mg/kg, according to the discretion of the attending anesthesiologist. Anesthesia was maintained with sevoflurane in oxygen/air mixture. Controlled ventilation with tidal volume of 6 to 8 mL/kg was applied. Peak inspiratory pressure and end-tidal carbon dioxide were maintained <25 cmH_2O and <40 mmHg, respectively. After LMA placement, the cuff pressure was measured and kept <60 cmH_2O by manometer measurement and periodically measured at 60-minute interval there after. Intraoral suctioning was performed as needed. At the end of the operation, neostigmine and atropine were given for reversal of muscle relaxant. LMA was removed after the patient was fully awake with adequate spontaneous breathing.

Data collection

Patient characteristics and perioperative data, including age, gender, body weight, height, ASA physical status, anesthesia personnel who performed LMA insertion, number of insertion attempts, LMA cuff pressure, operation time, and intraoperative opioid consumption were recorded. Sorethroat symptom which defined as constant pain or discomfort in the throat independent of swallowing[13] was evaluated at the first and the forth postoperative hour by a member of research team who was blinded to the patient's group. Sorethroat pain was measured using a verbal numerical rating scale (VNRS) that ranged from 0 to 10, with 0 signifying no pain and 10 being reflective of the worst possible pain. Complications including dysphagia, dysphonia and serious airway complications such as trauma to upper airway, aspiration of gastric content, airway obstruction or laryngospasm were recorded. The local adverse effects of BH[1], such as local numbness, local stinging sensation or throat irritation were also recorded. Patient satisfaction to anesthesia was assessed at the fourth postoperative hour using VNRS that ranged from 0 to reflect the highest level of dissatisfaction to 10,which reflected the highest level of satisfaction.

Statistical analysis

Based on previous study[1], the incidence of patients without POST after general anesthesia using LMA lubricated with salineat the first postoperative hour was 66%. Using an nQuery program, a sample size of 36 patients per group would allow detecting a 40% increase in the incidence of patient without POST with 80% power at the *p*-value of 0.05. Assuming an estimated 10% drop rate, 40 subjects per group were enrolled.

Data were analyzed using PASW Statistics for Windows, 18.0 Chicago: SPSS Inc. Categorical variables were presented as number (%), and were compared between groups using Chi-square test or Fisher's exact test, as appropriate. Continuous variables were presented as mean $\pm$ standard variation (SD) or

median with 25th and 75th percentile (P_{25} and P_{75}), and were compared between groups using unpaired Student's t-test or Mann-Whitney U test, as appropriate. A *p*-value of <0.05 was regarded as being statistically significant.

Results

Eighty patients were enrolled in this study (Fig. 1). There was no statistically significant difference in age, gender, BMI, ASA physical status, anesthesia personnel who performed LMA insertion, number of insertion attempts, LMA cuff pressure, operation time,or intraoperative opioid consumption between the groups (Table 1).

Table 2 showed the incidence and severity of POST. The incidences of patient without POST at the first and the forth postoperative hour in Group BH were higher than those in Group C (47.5% vs. 27.5%, $p = 0.07$ and 82.5% vs. 60.0%, $p = 0.03$, respectively). The median (P_{25}, P_{75}) VNRS for POST at the first and the forth postoperative hour in Group BH were lower than those in Group C [2 (0, 4) vs. 4 (0, 5), $p = 0.01$ and 0 (0, 0) vs. 0 (0, 2), $p = 0.02$, respectively]. At the forth postoperative hour, there was a 22.5% (95% CI 3.3 to 41.7) absolute increase in the incidence of patients without POST and this translated to a number needed to treat (NNT) of 4.4 (95% CI 2.4 to 30.4). Two patients in Group BH and two patients in Group C experienced dysphonia and dysphagia, respectively (Table 2). No serious airway complications or major adverse reactions related to BH were observed. The median (P_{25}, P_{75}) VRNS for patient satisfaction in Group BH was higher than that in Group C [9.0 (9, 10) vs. 8.5 (8, 9), $p<0.01$].

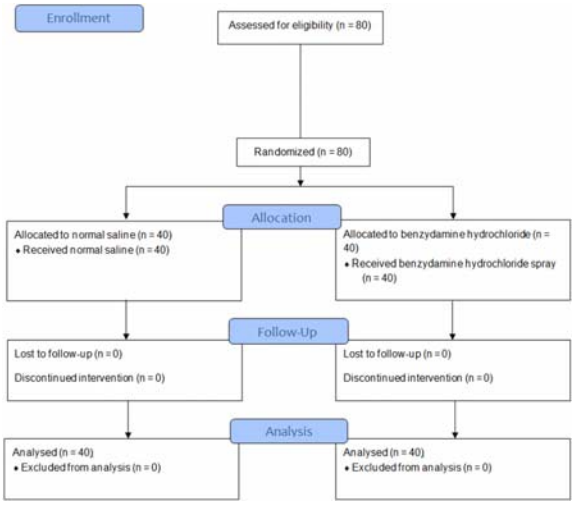

Fig. 1 Consort flow.

Discussion

This study demonstrated that pre-insertion spray of BH over LMA cuff resulted in higher number of patients with no POST at the forth postoperative hour when compared to placebo (NSS spray). However, this reduction in POST was not shown in the first postoperative hour. The late onset of BH spray could be explained by its pharmacokinetics. Previous study by Baldock et al[14] shown that peak plasma concentration can be achieved at 3.60±0.89 hours following BH mouth wash and the half-life was as long as 9.4±2.9 hours.

It was observed that, in both groups, the severity of POST was intense immediate after surgery but subsequently improved thereafter. This might be due to multifactorial causes such as effects from emergence, anticholinergic effects of reversal agents, or oropharyngeal suctions. Nevertheless, the severity of POST at the first and the forth postoperative hour were significantly lesser in Group BH compared with Group C. In the recent meta-analysis, Chen et al[15] concluded that POST could be significantly reduced by prophylactic application of topical BH to either the airway devices or to the patient's oral cavity without any major BH-related complications. This present study found the similar results.

At the first postoperative hour, there was a trend in increased number of patients without POST in Group BH compared with Group C, although the difference was statistically significant at the forth postoperative hour. The incidence of patients without POST at the first and the forth postoperative hour in Group BH in this study was lower than those previously reported by Kati et al[1] (47.5% vs. 96% and 82.5% vs. 96%, respectively). Moreover, the 20% and 22.5% absolute increase in the number of patients without POST at the first and the forth postoperative hour observed in this present study was lower than those reported by Kati et al[1], and lower than expectation of 40%. This might be due to the different methods of applying BH (LMA cuff vs. direct to posterior pharyngeal wall prior to LMA insertion). BH spayed on to the LMA cuff was the technique selected for this study to avoid direct application of medication to the patient's oral cavity, which might result in numbness, tingling, abnormal sensation, and other types of throat-related discomfort. In addition, medication sprayed directly onto the LMA cuff would act more directly and have better analgesic and anti-

Table 1. Demographicand clinical characteristics and laryngeal mask airway parameters

	Group C (n = 40)	Group BH (n = 40)
Age (y)	46.4±14.9	49.1±16.0
Gender: Female	20 (50.0)	23 (57.5)
Body mass index (kg/m^2)	24.0±3.5	23.3±3.4
ASA physical status		
I	19 (47.5)	13 (32.50)
II	18 (45.0)	22 (55)
III	3 (7.5)	5 (12.50)
Anesthesia personnel who performed LMA insertion		
Nurse anesthetist student	15 (37.5)	15 (37.50)
Anesthesia resident	21 (52.5)	17 (42.50)
Nurse anesthetist	4 (1.0)	6 (15)
Anesthesiologist	0 (0.0)	2 (5)
Number of insertion attempts		
1	37 (92.5)	35 (87.5)
2	2 (5.0)	4 (10.0)
3	1 (2.5)	1 (2.5)
Average LMA cuff pressure (cmH_2O)	40.0±9.5	43.8±9.1
Operation time (min)	110.2±53.2	95.3±49.6
Intraoperative morphine milligram equivalent consumption (mg)	10.0±3.4	9.5±3.7

Data presented as mean ± SD or n (%)
ASA = American Society of Anesthesiologists, LMA = Laryngeal mask airway

Table 2. Number of patients without postoperative sore throat (POST) andseverity of POST

	Group C (n = 40)	Group BH (n = 40)	*p*-value
Number of patients without POST			
At 1st postoperative hour	11 (27.5)	19 (47.5)	0.07
At 4th postoperative hour	24 (60.0)	33 (82.5)	0.03
POST VNRS			
At 1st postoperative hour	4 (0,5)	2 (0,4)	0.01
At 4th postoperative hour	0 (0,2)	0 (0,0)	0.02

Data presented as median (P_{25}, P_{75}) or n (%)
P_{25} = 25th percentile; P_{75} = 75th percentile; VNRS=Verbal Numerical Rating Scale

inflammatory effects on the affected mucosa, as opposed to a more generalized approach to application of BH in patient's oral cavity. Another possible factor might be due to the experience of the personal who applied the LMA. In this study, most of the cases were applied by the anesthesia trainees but Kati et al[1] did not mention about this regard.

The number needed to treat of 4.4 to increase the incidence of patients without POST at the forth postoperative hour found in this study was indicative of a highly cost-effective technique. No patients in either group experienced severe POST or any serious adverse effects from using BH. The only airway complications reported were two patients with dysphonia in the BH group and two patients with dysphagia in the control group. Neither condition required any specific treatment and all patients recovered well prior to discharge. Unlike the results from the study by Kati et al[1], which reported 8.0% of patients received BH spayed at pharyngeal mucosa experienced local numbness and throat irritation, there was no such complaint in Group BH in the present study, and this might relate to high level of overall patient satisfaction.

There were some limitations in this study should be mentioned. First, there was no previous study to guide the appropriate dose of BH sprayed onto the LMA cuff. In this study, four puffs of BH were sprayed on the LMA cuff based on the manufacturer's recommended dose for treatment of pharyngitis and tonsillitis. Increasing the amount of BH sprayed onto the LMA may improve patient outcomes. However, any increase in the amount of BH used should be weighed against any potential risk of BH-related side effects. In addition and as mentioned earlier, different techniques of application of BH should be investigated to determine if there are any differences in efficacy or adverse effects between techniques. Second, variation in experience among anesthesia personnel inserting LMA might influence the degree of pharyngeal tissue trauma and subsequent occurrence of POST. Third, analgesic agents received during postoperative period were not recoded. Nevertheless, assuming that there was no difference in postoperative pain management between the groups and according to the pharmacokinetics of topical BH, the increased number of patients without POST in Group BH at the fourth postoperative hour should reflect the efficacy of BH spayed. Fourth and lastly, although no adverse effects related to BH were observed, it is possible that the sample size was too small to detect any rare a forementioned adverse effects from this medication.

Conclusion

BH sprayed on the LMA cuff increased the number of patients without POST at the forth postoperative hour, and reduced the severity of POST at the first and fourth postoperative hours. This technique yielded high patient satisfaction and cost-effectiveness with an NNT of 4.4.

What is already known on this topic?

0.3% BH sprayed, a NSAID, can effectively reduce POST in patients undergoing general anesthesia with endotracheal tube and LMA by spraying onto the endotracheal cuff or patient's oral cavity. However, there were 10% of patients reported local numbness and tingling sensation following topical BH.

What this study adds?

0.3% BH sprayed on LMA cuff increased the number of patients without POST, decreased severity of POST, and increased patient satisfaction after general anesthesia using LMA without adverse effect reported.

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Trial registration

ClinicalTrials.in.th: TCTR 20161127002.

Potential conflicts of interest

None.

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ยาเบนไซดรามีนไฮโดรคลอไรด์ช่วยลดอาการเจ็บคอในผู้ป่วยที่มารับการระงับความรู้สึกแบบทั้งตัวโดยใช้อุปกรณ์ช่วยหายใจชนิดฝาครอบกล่องเสียง

สถิตย์ ชัยรัตนวานิช, อรรณพ พิริยะแพทย์สม, ประไพรัตน์ เหมราช, สุกัญญา จิระชัยพิทักษ์, ณัฐวุฒิ มณีขัตย์, อภิชาต ศุภธรรมวิทย์

วัตถุประสงค์: *เพื่อพิสูจน์ว่าการพ่นเบนไซดรามีน ไฮโดรคลอไรด์ ที่อุปกรณ์ช่วยหายใจชนิดฝาครอบกล่องเสียงสามารถเพิ่มจำนวนผู้ป่วยที่ไม่มีอาการเจ็บคอภายหลังการระงับความรู้สึกแบบทั้งตัวโดยได้*

วัสดุและวิธีการ: *ผู้ป่วยจำนวน 80 คน ที่มาเข้ารับการระงับความรู้สึกแบบทั้งตัวโดยใช้อุปรณ์ช่วยหายใจชนิดฝาครอบ กล่องเสียงถูกสุ่มเป็น 2 กลุ่มเท่า ๆ กัน ได้แก่ กลุ่มพ่นเบนไซดรามีน ไฮโดรคลอไรด์ และกลุ่มพ่นน้ำเกลือที่อุปกรณ์ช่วยหายใจชนิดฝาครอบกล่องเสียง ผู้ป่วยจะถูกประเมินอาการเจ็บคอ ณ เวลา 1 และ 4 ชั่วโมงภายหลังการระงับความรู้สึก ข้อมูลของผู้ป่วย การผ่าตัด การระงับความรู้สึก คะแนนความปวด ภาวะแทรกซ้อนบริเวณทางเดินหายใจ และความพึงพอใจโดยรวมจะถูกบันทึกและนำมาสรุปผล*

ผลการศึกษา: *อุบัติการณ์ของผู้ป่วยที่ไม่มีอาการเจ็บคอที่ 1 และ 4 ชั่วโมงภายหลังการระงับความรู้สึกในกลุ่มพ่นเบนไซดรามีน ไฮโดรคลอไรด์สูงกว่ากลุ่มพ่นน้ำเกลือ (ร้อยละ 47.5 เทียบกับ ร้อยละ 27.5, p = 0.07 และร้อยละ 82.5 เทียบกับ ร้อยละ 60.0, p = 0.03 ตามลำดับ) ผู้ป่วยในกลุ่มพ่นเบนไซดรามีน ไฮโดรคลอไรด์มีความรุนแรงของอาการเจ็บคอต่ำกว่ากลุ่มพ่นน้ำเกลือ ณ เวลา 1 และ 4 ชั่วโมงภายหลังการระงับความรู้สึก อย่างมีนัยสำคัญ จำนวนผู้ป่วยที่ไม่เจ็บคอในกลุ่มพ่นเบนไซดรามีน ไฮโดรคลอดไรด์ ที่ชั่วโมงที่ 4 ภายหลังการระงับความรู้สึกเพิ่มขึ้นมากกว่ากลุ่มพ่นน้ำเกลือร้อยละ 22.5 (95% CI 3.3 ถึง 41.7%) คิดเป็นจำนวนผู้ป่วยต่อการรักษา 4.4 คน ไม่พบภาวะแทรกซ้อนรุนแรงบริเวณทางเดินหายใจหรือผลข้างเคียงจากยาเบนไซดรามีน ไฮโดรคลอดไรด์ ในทั้ง 2 กลุ่ม ความพึงพอใจต่อการระงับความรู้สึกในกลุ่มพ่นเบนไซดรามีน ไฮโดรคลอดไรด์สูงกว่ากลุ่มพ่นน้ำเกลือ*

สรุป: *การพ่นยาเบนไซดรามีน ไฮโดรคลอไรด์ ที่อุปกรณ์ช่วยหายใจชนิดฝาครอบกล่องเสียงสามารถเพิ่มจำนวนผู้ป่วย ที่ไม่เจ็บคอภายหลังการระงับความรู้สึกแบบทั้งตัว ช่วยลดความรุนแรงของอาการเจ็บคอและเพิ่มความพึงพอใจต่อการระงับความรู้สึกได้*