Efficacy of Benzydamine Hydrochloride Dripping at Endotracheal Tube Cuff for Prevention of Postoperative Sore Throat

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Background: *Postoperative sore throat (POST) is a frequent consequence following ETT intubation, which may negatively affect the postoperative course and patient satisfaction. Benzydamine hydrochloride is a topically-applied non-steroidal anti-inflammatory drug (NSAID). The authors evaluated the analgesic effect of benzydamine hydrochloride dripping on the ETT cuff on POST.*

Material and Method: *Eighty-six patients participated in this randomized controlled trial. They were assigned into either the benzydamine hydrochloride or the control group. The whole ETT cuff was dripped either with 3 ml (4.5 mg) of benzydamine hydrochloride or nothing five minutes prior to anesthesia induction. The incidence and severity of POST at 0, 2, 4, 6, 12, and 24 hours postoperatively were assessed. The potential adverse effects of benzydamine hydrochloride (throat numbness, throat burning sensation, dry mouth, and thirst) were also evaluated.*

Results: *Twenty-five patients (58.14%) in each group had POST (p-value = 1). The severity of POST (calculated from affected patients) in both groups at different time points was not significantly different. Patients in the benzydamine hydrochloride group did not have a higher incidence of adverse effects.*

Conclusion: *We found that dripping benzydamine hydrochloride on the ETT cuff neither reduced the incidence of POST nor increased the incidence of adverse effects in comparison with no intervention.*

Keywords: *Benzydamine hydrochloride, Endotracheal tube, Postoperative sore throat*

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Postoperative sore throat (POST) after tracheal intubation is common[1] and is certainly one of the leading postoperative patient complaints[2]. The use of a smaller-sized endotracheal tube (ETT)[3] and the appropriate control of the ETT pressure with a manometer have been found to reduce the incidence of POST[4]. Female sex[1,5], older age[5], history of smoking or lung pathology[1], higher grade of difficulty in intubation[5], duration of anesthesia or operation[1,5], intraoperative patient positioning[5], postoperative nausea and blood stains on the teeth and/or the ETT[1] are factors responsible for POST. A significant number of modalities (drugs and methods of administration) have been tried to reduce the incidence of POST with various results. These include NSAIDs[6-12], local anesthetics[13-17], ketamine[18], chamomile-extract[19,20], Strepsils®[21] and benzydamine hydrochloride[22-25].

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Benzydamine hydrochloride is a topical anti-inflammatory drug with antipyretic, analgesic, and antimicrobial effects[23]. However, it has distinctly different physicochemical characteristics and pharmacological properties from those of the aspirin-like non-steroidal anti-inflammatory drugs. Benzydamine hydrochloride is widely used for local application with no serious adverse effects[26].

Because POST is unpleasant to patients, the authors conducted this study to evaluate the analgesic effects of benzydamine hydrochloride dripping along the cuff of the ETT on POST.

Material and Method

The present study was approved by our institutional ethics committee. The authors included only patients who were willing to participate and all of them gave an informed consent. The calculation of the sample size was based on the study of Hung et al[23] which found that at six hours after extubation, 17% of patients in benzydamine hydrochloride group had POST while 40.8% of patients in saline group had

POST. Thirty-nine patients were required for each group to achieve a 95% confidence interval and an 80% power. The authors enrolled 86 patients in this prospective, double-blind, randomized, and controlled trial. Our inclusion criteria were patients aged 18 to 65 years, ASA status I-II, Mallampati grade I-II, duration of surgery less than four hours and placed in the supine position. Patients with any of the following were excluded, undergoing oral, cervical spine or thyroid surgery, more than one attempt of ETT intubation or intubated with a technique of rapid sequence induction with cricoid pressure, insertion of nasogastric/orogastric tube or esophageal stethoscope, complaint of sore throat or hoarseness, presence of upper respiratory tract infection within seven days prior to the operation, gastroesophageal reflux and known allergy to benzydamine hydrochloride, or other non-steroidal anti-inflammatory drugs (NSAIDs).

Based on computer-generated randomization, all of the patients were randomly assigned by picking sealed code envelopes into two groups, the benzydamine hydrochloride group (BH) and the control group (C). A sterile ETT with a high-volume and low-pressure cuff was used. An ETT with an internal diameter of 7.5 mm (ID 7.5) and 7.0 mm (ID 7.0) was inserted in male and female patients, respectively. The application of either benzydamine hydrochloride (Difflam, Inova Pharmaceutical, Australia, 22.5 mg in 15 ml or 1.5 mg/ml) or NSS to the ETT cuff was performed 5 minutes prior to the induction of anesthesia. In the BH group, we dripped 0.5 ml of benzydamine hydrochloride solution on the ETT cuff and rotated the ETT 60 degrees. After that, we dripped another 0.5 ml of benzydamine hydrochloride solution and then rotated the ETT another 60 degrees. The same procedure was repeated until a total of 3 ml (4.5 mg) of benzydamine hydrochloride solution was applied and a total rotation of 360 degrees was completed. By contrast, in the C group, nothing was applied onto the ETT cuffs. All of the patients were monitored on a standard basis and oxygen was administered via a face mask. After intravenous administration of either morphine or fentanyl, induction was accomplished by either propofol or thiopental, and either rocuronium, vecuronium or cisatracurium was chosen as a muscle relaxant. An ETT was inserted by an anesthesiology consultant or a resident with at least 12 months of experience in ETT intubation. The ETT cuff was inflated with room air using the just-sealed technique. Balanced anesthesia was maintained, while nitrous oxide was not used in all of the cases. At the end of the operation, the neuromuscular blockade was reversed by neostigmine and atropine. After full awakening, the ETT was removed after gentle suctioning of oral secretions. All of the patients were carefully transferred to the Postanesthesia Care Unit. At 0, 2, 4, 6, 12, and 24 hours after extubation, each patient was asked about the presence of POST. The severity of POST was graded on a verbal numerical rating scale (VNRS) of 0-10. The patients who had VNRS more than 0 at any assessment time was counted as experiencing POST. The perioperative data comprising type of operation, duration of operation/anesthesia, personnel who performed the intubation, larygoscopic view grading, use of oral airway/stylets, intraoperative consumption of morphine/fentanyl, presence of blood stains on the ETT, coughing upon extubation, and performing of tracheal suctioning were recorded. The postoperative data were also evaluated and they consisted of the presence of coughing, hoarseness, postoperative nausea and vomiting (PONV) as well as use and administration routes of analgesics. The potential adverse effects of benzydamine hydrochloride (throat numbness, throat burning sensation, dry mouth, and thirst) were also assessed.

The continuous data with normal distribution were analyzed using the un-paired student's t-test and those with non-normal distribution via the Mann-Whitney U test. The categorical data were analyzed by means of the Chi-square test and the Fisher's exact test was employed if the expected values were less than 5. The data with normal distribution were expressed as mean ± SD and those with non-normal distribution as median (range). P-values of <0.05 were considered statically significant.

Results

The consort flow chart of the present study is illustrated in Fig. 1 and the characteristics of its population are demonstrated in Table 1. No significant differences were found between the two groups in terms of sex, age, body mass index (BMI), smoking, preoperative use of NSAIDs, ASA classification and Mallampati grading. Table 2 shows that the peri-operative data were not significantly different in terms of duration of the operation, experience of practitioners performing the ETT intubation, laryngoscopic view grading, use of oral airway and stylets, intraoperative consumption of opioids (morphine, fentanyl), blood stains on the ETT upon extubation, coughing upon extubation and presence of tracheal suctioning.

Twenty-five patients (58.14%) from each group experienced POST (p-value = 1). The intensity of POST (calculated only from patients affected with POST) at 0, 2, 4, 6, 12 and 24 hours following the operation as measured by the verbal numerical rating scale (0-10) is demonstrated in Fig. 2; no significant differences were found. The postoperative data obtained while the patients were admitted in the wards are presented in Table 3. No significant differences were found in terms of the presence of coughs, hoarseness and postoperative nausea and vomiting (PONV) as well as degrees of consumption and routes of administration of analgesics. The data on potential adverse effects of the local application

Table 1. Characteristics of the study population

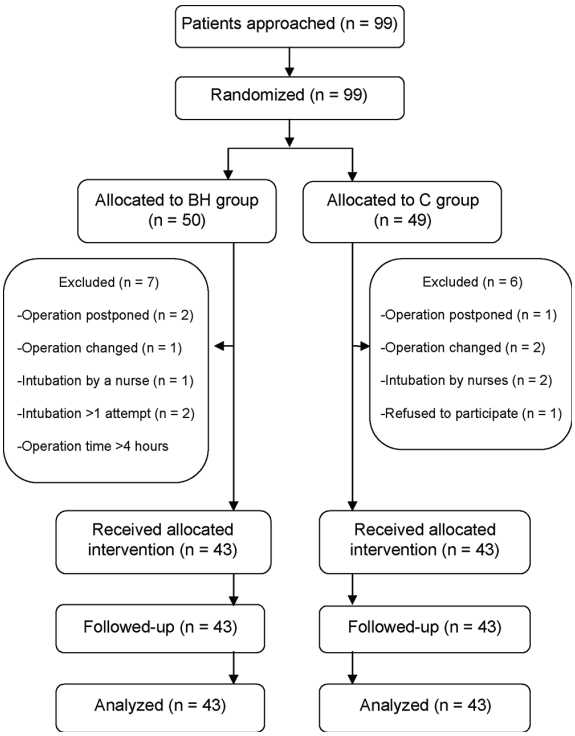
Group	Benzydamine HCl (n = 43)	Control (n = 43)	p-value
Sex (n, %)			
Male	4 (9.3)	8 (18.6)	0.35
Female	39 (90.7)	35 (81.4)	
Age (years)			
Mean ± SD	42.0±10.9	41.0±11.2	0.70
BMI (kg/m^2)			
Mean ± SD	24.2±4.0	22.6±3.8	0.07
Smoking (n, %)	1 (2.3)	6 (14.0)	0.11
Preoperative use of NSAIDs (n, %)	2 (4.7)	1 (2.3)	1
ASA classification (n, %)			
I	8 (18.6)	8 (18.6)	1
II	35 (81.4)	35 (81.4)	
Mallampati grading (n, %)			
I	8 (18.6)	11 (25.6)	0.60
II	35 (81.4)	32 (74.4)	

Benzydamine HCl = benzydamine hydrochloride; BMI = body mass index; NSAIDs = nonsteroidal anti-inflammatory drugs; ASA = American Society of Anesthesiologists; SD = standard deviation

Table 2. Perioperative data of the study population

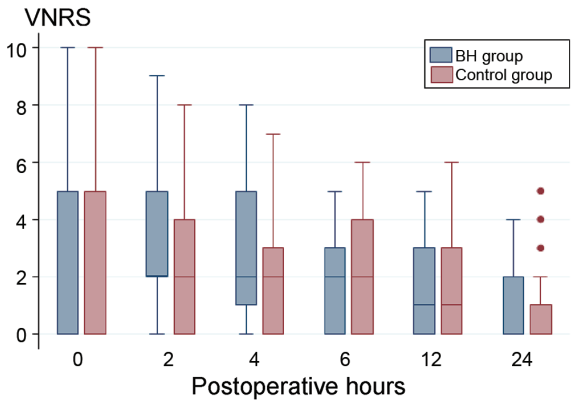
Group	Benzydamine HCl (n = 43)	Control (n = 43)	p-value
Duration of surgery (minutes)			
Mean ± SD	108.7±47.9	110.1±51.7	1
Endotracheal tube inserted by (n, %)			
Residents	10 (23.3)	9 (20.9)	1
Consultants	33 (76.7)	34 (79.1)	
Laryngoscopic view grading (n, %)			
I	22 (51.2)	28 (65.1)	0.07
II	12 (27.9)	13 (30.2)	
III	9 (20.9)	2 (4.7)	
Use of oral airway (n, %)	10 (23.3)	8 (18.6)	0.79
Use of stylet (n, %)	0 (0)	1 (2.3)	1
Intraoperative use of [mean ± SD]			
Morphine (mg)	6.5±4.9	5.8±5.2	0.50
Fentanyl (mcg)	53.6±65.1	61.7±66.5	0.57
Blood strain on ETT (n, %)	6 (14.0)	11 (25.6)	0.28
Coughing on extubation (n, %)	28 (65.1)	25 (58.1)	0.66
Tracheal suctioning (n, %)	8 (18.6)	14 (32.6)	0.22

Benzydamine HCl = benzydamine hydrochloride; SD = standard deviation; ETT = endotracheal tube



BH = benzydamine hydrochloride; C = control

Fig. 1 The consort flow chart of the study.



VNRS = verbal numerical rating score; BH = benzydamine hydrochloride

Fig. 2 The intensity of postoperative sore throat (POST) in the first 24 hours after the operation.

of benzydamine hydrochloride are shown in Table 4. There were no significant differences between the two groups in regards to throat numbness, throat burning sensation, dry mouth, and a feeling of thirst.

Discussion

The present study revealed that dripping 3 ml of benzydamine hydrochloride solution onto the cuff of the ETT 5 minutes prior to intubation did not reduce the incidence and severity of POST in the first 24 hours postoperatively. The incidence of potential adverse effects related to benzydamine hydrochloride in the study group was not higher than that of the control group.

POST is commonly found in patients inserted with an ETT or a laryngeal mask airway (LMA). A face-to-face interview with 12,276 patients demonstrated 1,228 complaints (10%) of sore throat[2]. Another prospective follow-up study among

Table 3. Postoperative data of the study population

Group	Benzydamine HCl (n = 43)	Control (n = 43)	p-value
Coughing (n, %)	7 (16.3)	13 (30.2)	0.20
Hoarseness (n, %)	13 (30.2)	17 (39.5)	0.50
PONV (n, %)	18 (41.9)	17 (39.5)	1
Routes of analgesics (n)			
Oral	34	36	0.78
IV intermittent boluses	29	30	1
IV continuous infusion	0	1	1
Epidural	1	0	1
Postoperative analgesics (n)			
Morphine/fentanyl	28	30	0.82
Tramadol	1	3	0.62
NSAIDs/COXIBs	22	24	0.83
Paracetamol	26	30	0.50

Benzydamine HCl = benzydamine hydrochloride; PONV = postoperative nausea and vomiting; IV = intravenous; NSAIDs = nonsteroidal anti-inflammatory drugs; COXIBs = selective cyclo-oxygenase II inhibitors

Table 4. Potential adverse effects of benzydamine hydrochloride

Group	Benzydamine HCl (n = 43)	Control (n = 43)	p-value
Throat numbness (n, %)	2 (4.7)	5 (11.6)	0.43
Throat burning (n, %)	7 (16.3)	4 (9.3)	0.52
Dry mouth (n, %)	27 (62.8)	24 (55.8)	0.66
Thirst (n, %)	27 (62.8)	26 (60.5)	1

Benzydamine HCl = benzydamine hydrochloride

809 patients found an incidence of 40% for the occurrence of POST[1]. Various factors have been identified as POST-responsive factors[1-5]. Causative events thought to be related to POST include: (a) injury to pharyngolaryngeal mucosa, (b) swelling of posterior pharyngeal wall, (c) swelling of vocal cords, (d) dehydration of mucosa, (e) effect of cuff pressure on perfusion pressure of mucosa[24].

POST leads to airway discomfort and may affect the satisfaction of patients at large. Many analgesics and methods of administration have been tried to prevent or reduce the occurrence of POST; benzydamine hydrochloride is one of those. Benzydamine hydrochloride is a locally applied NSAID possessing not only analgesic and antipyretic properties, but also an antimicrobial effect[23]. Benzydamine hydrochloride is a liquid and is used topically; therefore, a range of methods of administration have been employed including delivery of the drug to either the airway mucosa[24,25] or the ETT cuff[22,23].

Our study did not find any beneficial effects of dripping benzydamine hydrochloride on the ETT cuff on POST. Gulhas et al demonstrated that spraying benzydamine hydrochloride into the oral cavity 30 minutes before the operation and repeating the same procedure at 5 minutes before the induction of anesthesia did not reduce the incidence of POST in comparison to the application of distilled water[24]. Even though the methods of delivery of benzydamine hydrochloride between the two studies were different, the results were accordingly similar.

On the other hand, it has been demonstrated that spraying benzydamine hydrochloride on the ETT cuff reduces the incidence and severity of POST[22,23] without causing more benzydamine hydrochloride-related side effects[22]. The gargling of benzydamine hydrochloride for 30 seconds, 5 minutes prior to anesthetic induction, has been shown as significantly effective in reducing the incidence and severity of POST[25].

As far as the authors know, the present study is the first one employing the dripping of benzydamine hydrochloride solution onto the ETT cuff. The method of application of benzydamine hydrochloride may explain the present study's negative result but the authors do not think the method of delivery of benzydamine hydrochloride plays a considerable role because, with either technique, the ETT cuff was surrounded with the drug. Other supporting evidence that the methods of administration may not significantly influence the effects of benzydamine hydrochloride on POST is the finding that topical spray of the drug into the oral cavity does not help to reduce the incidence of POST[24], while a similar method of delivery, the gargling of benzydamine hydrochloride, significantly lowers the incidence and intensity of POST[25].

When considering the dosage of benzydamine hydrochloride, we used 4.5 mg, while Huang et al, used 0.75 mg[22] and Hung et al, used 1.5 mg[23]. Therefore, the authors think that our dose was not inadequate, so the dose is unlikely to be the key factor for the prevention or reduction of POST.

Conclusion

The present study demonstrated no analgesic effect of benzydamine hydrochloride dripping on the ETT cuff on reducing the incidence of POST in comparison to the control group, which received no intervention. The severity of POST among affected patients was not statistically different. Likewise, the incidence of potential adverse effects related to benzydamine hydrochloride was not statistically different between the two groups.

Potential conflicts of interest

None.

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ประสิทธิภาพของการหยดเบนซีดามีนไฮโดรคลอไรด์บนถุงลมของท่อหายใจต่อการป้องกันการเกิดอาการเจ็บคอหลังการผ่าตัด

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ภูมิหลัง: *อาการเจ็บคอหลังการผ่าตัดเป็นอาการที่เกิดขึ้นบ่อยหลังการใส่ท่อหายใจ ซึ่งมีผลกระทบต่อความพึงพอใจของผู้ป่วย เบนซีดามีนไฮโดรคลอไรด์เป็นยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ซึ่งสามารถให้บนเยื่อบุได้ การศึกษานี้เพื่อประเมินผลการระงับปวดของเบนซีดามีนไฮโดรคลอไรด์ที่หยดบนถุงลมของท่อหายใจต่อการเกิดอาการเจ็บคอหลังการผ่าตัด*

วัสดุและวิธีการ: *แบ่งผู้ป่วย 86 ราย ออกเป็น 2 กลุ่ม คือ กลุ่มควบคุมที่ไม่มีการหยดสิ่งใด ๆ บนถุงลมของท่อหายใจ และกลุ่มเบนซีดามีนไฮโดรคลอไรด์ซึ่งมีการหยดสารละลายเบนซีดามีนไฮโดรคลอไรด์ 3 มล. (4.5 มก.) บนถุงลมของท่อหายใจ 5 นาที ก่อนเริ่มนำสลบ ประเมินอัตราการเกิดและความรุนแรงของอาการเจ็บคอหลังการผ่าตัดที่ 0, 2, 4, 6, 12 และ 24 ชั่วโมงหลังการผ่าตัด รวมทั้งประเมินการเกิดผลข้างเคียง ได้แก่ ชาในลำคอ ปวดแสบร้อนระคายเคืองในลำคอ ปากแห้ง และอาการกระหายน้ำ*

ผลการศึกษา: *ผู้ป่วย 25 ราย ของแต่ละกลุ่ม (ร้อยละ 58.14) มีอาการเจ็บคอหลังการผ่าตัด (p-value = 1) ความรุนแรงของอาการเจ็บคอที่แต่ละเวลาของผู้ป่วยทั้ง 2 กลุ่ม ไม่แตกต่างกัน ผู้ป่วยในกลุ่มเบนซีดามีนไฮโดรคลอไรด์เกิดผลข้างเคียงไม่แตกต่างจากกลุ่มควบคุม*

สรุป: *การหยดสารละลายเบนซีดามีนไฮโดรคลอไรด์บนถุงลมของท่อหายใจ ไม่ลดอุบัติการณ์ของการเกิดอาการเจ็บคอหลังการผ่าตัด รวมทั้งไม่เพิ่มการเกิดผลข้างเคียงด้วย*