Licorice versus ketamine gargle for postoperative sore throat due to insertion of a double-lumen endobronchial tube

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Background
Postoperative sore throat (POST) is common after tracheal intubation, especially with double-lumen endobronchial tube (DLT). Licorice has many uses such as dental hygiene and in sore throat.Ketamine gargle is a newly proposed adjunct for reducing the incidence of POST in anesthesia. The aim of this study was to determine the efficacy of licorice and ketamine gargles in patients undergoing the insertion of DLT in preventing POST within 24 h.
Methods
This prospective, randomized, double-blind study included 90 patients undergoing thoracic surgery requiring DLT for one-lung ventilation. Patients were randomized to three groups (n=30) and were asked to gargle for 1 min to 15 min before operations. Group A received ketamine gargle (0.5 mg/kg ketamine in 30 ml of dextrose water 20%), group B received licorice gargle (500 mg licorice powder in 30 ml of dextrose water 20%), and group C (the control group) received 30 ml of dextrose water 20% gargle.Assessment of patients for the incidence and the severity of POST and any side effect was carried out in the recovery room. Sore throat (yes/no) and severity of its pain measured using visual analogue scale were recorded at baseline in the recovery room and then at 2, 4, and 24 h after operation with a specified questionnaire.
Results
The incidence of sore throat was significantly higher in group C at all time points in comparison with the other two groups. There was a marked decrease in the incidence of sore throat in groups A and B, with no significant difference between them. The severity of POST pain was significantly higher in group C when compared with the other two groups, with no significant difference between them and with no complications.
Conclusion
Ketamine and licorice gargles decrease the incidence and severity of sore throat occurring postoperatively due to DLT intubation, with no significant differences between them.

Keywords:
double-lumen endobronchial intubation, ketamine gargle, licorice gargle, sore throat

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Introduction

Postoperative sore throat (POST), cough, and hoarseness of voice are common, uncomfortable sequelae after tracheal intubation. Even though they are minor complications, they may cause significant postoperative morbidity and patient dissatisfaction [1].

These effects are likely to be due to irritation and inflammation of the airway as a result of trauma of the airway mucosa [2].

The double-lumen endobronchial tube (DLT) used for one-lung ventilation is more likely to cause a higher incidence of POST compared with a bronchial blocker inserted through a standard tracheal tube [3]. Moreover, although silicone DLTs are associated with a lower incidence of sore throat compared with polyvinyl chloride DLTs [4], the latter are used routinely in the clinical setting.

The licorice has been used in gastrointestinal ulcer treatment, dental hygiene, antimicrobial action, antitumor action, and lung diseases such as dry cough, hoarseness, sore throat, bronchitis, and asthma [5,6].

Ketamine gargle is a newly proposed adjunct for reducing the incidence of POST in anesthesia. The gargle is hypothesized to provide analgesia due to its inhibition of *N*-methyl-d-aspartate (NMDA) receptors and agonist activity at opioid receptors located in the oral and the upper respiratory tract mucosa [7,8].

Gargling is a simple intervention that takes less than a minute and can be performed by most of the patients. The aim of this study was to determine the efficacy of licorice and ketamine gargles in patients undergoing the insertion of DLT in preventing POST within 24 h.

Methods

This study was a randomized clinical trial. After the approval of the Ethics Committee of the hospital and obtaining written informed consent from the patients, this study was conducted in a tertiary care center between October 2015 and April 2016. A total of 90 adult patients undergoing thoracic surgery requiring DLT intubation for one-lung ventilation were enrolled in the study. Patients were excluded if they had a sore throat, hoarseness, coagulopathy, a history of oral surgeries, or a known or predicted difficult airway. Patients who required postoperative mechanical ventilation were also excluded. It was a double-blinded study. Patients were randomized to three groups (n=30) with the help of computer-generated random number tables in opaque sealed envelopes prepared by an anesthesiologist who did not participate in the study. The envelopes were opened by the staff nurse.

On the basis of previous studies [9,10] patients were asked to gargle for 1 min to 15 min before operations. Patients in the ketamine group (group A) received ketamine gargle (0.5 mg/kg ketamine in 30 ml of dextrose water 20%), whereas patients in the licorice group (group B) received licorice gargle (500 mg licorice powder) in 30 ml of dextrose water 20%. The third group was the control group (group C) and received 30 ml of dextrose water 20% gargle. General anesthesia was induced 15 min after gargling. Patients were monitored for ECG, oxygen saturation (SpO_2%), end-tidal CO_2, and noninvasive blood pressure after entering the operation room. After monitoring, patients were preoxygenated with 5 l/min O_2 100% for 3–5 min. For premedication, midazolam 0.02 mg/kg and fentanyl 2 μg/kg were administered. Three minutes later, induction was performed by administering 5 mg/kg thiopental and 0.5 mg/kg atracurium. Intubation was performed under smooth direct laryngoscopy with a polyvinyl chloride DLT size 37 Fr for male and size 35 Fr for female patients. Anesthesia was maintained with sevoflurane 2–4% end-tidal concen tration in an air/oxygen mixture with intermittent fentanyl and atracurium administered as required. Immediately following intubation and repositioning, fiberoptic bronchoscopy was used to confirm the correct placement of the tube.

All intubations were performed by the same anesthesiologist. Endotracheal tube (ETT) cuff was inflated until no exhalation sounds or leak was heard. Cuff pressure was less than 20 mmHg and airway pressure was less than 30 cm H_2O in all patients using volume-controlled ventilation. At the end of the surgery, oxygen 100% was administered and residual neuromuscular block was antagonized with a combination of neostigmine 0.05 mg/kg and glycopyrolate 0.01 mg/kg. Extubation was performed after gentle suctioning of oral secretions when patients were fully recovered and able to obey commands. In the recovery room, patients only received O_2 5 l/min through face mask. Primary outcome was sore throat. Secondary outcome was pain scale measured using visual analogue scale (VAS) scores.

Assessment of patients for the incidence and the severity of POST and any side effect was carried out on arrival in the recovery room by the anesthesiologist in charge of the recovery room who was blinded to the group allocation. Sore throat (yes/no) and severity of its pain measured using VAS were recorded at baseline in the recovery room and then at 2, 4, and 24 h after operation with a specified questionnaire. If VAS was equal to or greater than 5 at any time, rescue analgesics would be administered.

Statistics

Data were presented as mean and SD. Statistical analysis was carried out using SPSS, v.20 (IBM, NewYork, USA). Unpaired Student's t-test, paired t-test, analysis of variance, and the χ^2-test was used. P less than 0.05 was considered as statistically significant.

Sample size

Sample size was estimated using sample size calculator software with 95% confidence interval, P=0.05, power of 80%, and the difference between two groups of 20% in primary outcome (sore throat) based on pilot study.

A sample size of 28 patients per group was required. Two patients in each group were added for possible dropouts.

Results

There were no significant differences between the three groups in terms of age, body weight, sex distribution, or duration of surgery (Table 1).

The incidence of sore throat was significantly higher in the control group (group C) at all time points in comparison with the other two groups. There was a marked decrease in the incidence of sore throat in

Table 1 Demographic data

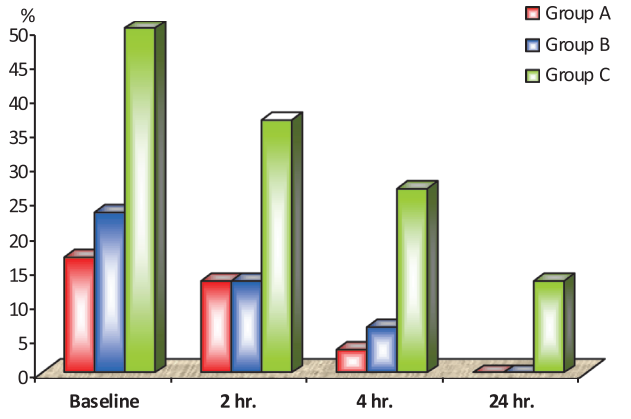
	Group A (*n*=30)	Group B (*n*=30)	Group C (*n*=30)	*T*-test	
				t	*P*-value
Age [mean (SD)] (years)	45.4 (3.7)	47.3 (4.2)	46.7 (3.9)	1.824	0.167
Sex [*n* (%)]					
Male	22 (73.3)	24 (80.0)	23 (76.7)	0.373	0.830
Female	8 (26.7)	6 (20.0)	7 (23.3)		
Body weight (mean±SD) (kg)	70.2 (4.8)	68.6 (5.2)	71.4 (4.3)	2.590	0.082
Duration of surgery [mean (SD)]	190.1 (17.5)	200.5 (16.8)	196.8 (16.7)	2.884	0.061

Table 2 Incidence of POST

Incidence of sore throat	Baseline	2 h	4 h	24 h
Group A [*N* (%)]	5 (16.7)	4 (13.3)	1 (3.3)	0 (0.0)
Group B [*N* (%)]	7 (23.3)	4 (13.3)	2 (6.7)	0 (0.0)
Group C [*N* (%)]	15 (50.0)	11 (36.7)	8 (26.7)	4 (13.3)
χ^2				
A and B				
χ^2	0.417	0.000	0.351	0.000
P-value	0.519	1.000	0.554	1.000
A and C				
χ^2	7.500	4.356	6.405	4.286
P-value	0.006*	0.037*	0.011*	0.038*
B and C				
χ^2	4.593	4.356	4.320	4.286
P-value	0.032*	0.037*	0.038*	0.038*

*Statistically significant.

Figure 1



Incidence of POST.

groups A and B, with no significant difference between them (Table 2 and Fig. 1).

The severity of POST pain was significantly higher in the control group when compared with the other two groups, with no significant difference between them (Table 3 and Fig. 2).

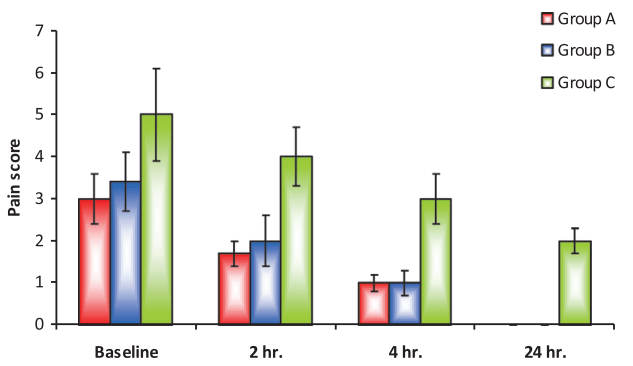
All patients received intravenous paracetamol (1 gm) every 8 h for 24 h starting from the time of reaching the recovery room. In addition to paracetamol, three patients

Table 3 Severity of POST pain

Pain score	Baseline	2 h	4 h	24 h
Group A [mean (SD)]	3 (0.6)	1.7 (0.3)	1 (0.2)	0.0 (0.0)
Group B [mean (SD)]	3.4 (0.7)	2 (0.6)	1 (0.3)	0.0 (0.0)
Group C [mean (SD)]	5 (1.1)	4 (0.7)	3 (0.6)	2 (0.3)
Analysis of variance				
f	48.932	149.681	244.898	331.334
P-value	<0.001*	<0.001*	<0.001*	<0.001*
A and B	0.075	0.107	1.000	1.000
A and C	<0.001*	<0.001*	<0.001*	<0.001*
B and C	<0.001*	<0.001*	<0.001*	<0.001*

*Statistically significant.

Figure 2



Severity of POST pain.

in the control group, two patients in group A, and three patients in group B required rescue analgesics on reaching the recovery room because of severe POST. A short-acting analgesic was given (pethidine 25 mg intravenously) so as to not affect the next set of observations. There were no complications related to the administration of the gargles.

Discussion

Findings in this study indicate that gargling with ketamine or licorice decreases the incidence and severity of POST in patients intraoperatively intubated with DLTs compared with the control group.

DLTs are commonly used for one-lung ventilation and are associated with a higher rate of laryngeal

complications, such as POST, compared with single-lumen ETTs [3,11].

The incidence of POST and hoarseness is directly correlated with the size of the ETT [4,12]. 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; and 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 [13].

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 [12].

Over the years, the anesthesiologists have used many methods to reduce POST, which include nonpharmacological and pharmacological trials with variable success. Nonpharmacological methods include the use of smaller-sized ETTs and lubricates. The pharmacological methods that have been used to reduce POST include the use of beclomethasone inhalation and gargling with medications [14–18].

Our study shows that ketamine gargle markedly decreased the incidence and severity of POST. Ketamine gargle analgesic effect in sore throat has been a matter of discrepancy in previous studies. Although some studies assured that ketamine gargle reduces the incidence of POST after endotracheal intubation [19,20], other studies showed little effect of ketamine gargle with the need to increase the dose of ketamine, which increased the incidence of ketamine adverse effects [21,22].

Ketamine blocks NMDA receptor. In addition, the decreased bronchomotor tone induced by ketamine is probably due to its interference with Ca^{2+} (a required step necessary to maintain the contraction) [23]. Recent reports on the incidence of POST following anesthesia have claimed that the incidence of POST does not necessarily reflect damage caused by the tracheal tube cuff but more of increased muscle contracture [24]. Sore throat and hoarseness that occur after total intravenous anesthesia with ketamine show that the systemic effect is not of much importance in alleviating sore throat. It is important to know that pre-emptive analgesia is a part of the bigger picture of decreasing pain [2].

In another study [25], serum ketamine and norketamine levels were measured at intervals up to 103 min after gargling. The authors reported that both levels were below those described to produce analgesia. Investigators have suggested that NMDA receptors are found not only in the central nervous system but also in the peripheral nerves. Moreover, experimental studies point out that peripherally administered NMDA receptor antagonists are involved in antinociception and anti-inflammatory cascade [26].

However, in most developing countries, the use of medicinal plants such as licorice have been observed as a normative basis for the maintenance of good health; 80% of the world population relies on herbal medicines as over-the-counter herbal formulation.

Licorice grows in subtropical climates in Europe, the Middle East, and Western Asia. It is derived from the root of glycyrrhiza glabra, which belongs to the leguminosae family [27].

Licorice contains a number of ingredients. Many of these, including glycyrrhizin, liquilitin, and glabridin, are reported to have anti-inflammatory and antiallergic properties, peripheral and central antitussive properties, and ulcer-healing properties, respectively [9].

In our study, gargling with licorice markedly decreased the incidence and severity of POST. This is in line with the finding of Agarwal *et al*. [9], who revealed that the severity of POST was reduced in the licorice group compared with the control group, both at rest (0, 2, and 4 h) and on swallowing at all time points (0, 2, 4, and 24 h) postoperatively.

However, in our study, no significant difference was recorded between ketamine and licorice gargles in decreasing POST incidence and severity. No side effects were recorded in all groups.

Conclusion

Ketamine and licorice gargles decrease the incidence and severity of sore throat occurring postoperatively due to DLT intubation, with no significant differences between them.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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