Original Article

Efficacy of Very Low Dose Intravenous Lidocaine in Preventing Cough and Sore Throat after Awakening from General Anesthesia: A Randomized Controlled Trial

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Objective: To evaluate the minimal dose of intravenous lidocaine (0.25 mg/kg) administered before extubation to prevent post-operative cough and sore throat.

Materials and Methods: The present study employed a prospective double-blinded randomized, control trial. Eighty-five patients scheduled for elective surgery were randomized to receive an intravenous lidocaine bolus of 0.25 mg/kg (treatment group), or 0.5 mg/kg (control group) at the end of anesthesia. The severity of cough and post-operative sore throat were evaluated by a blinded anesthesiologist.

Results: Forty-two patients were assigned to the treatment group and 43 patients to the control group. According to the non-inferiority margin in the present study of 10% compared with the high-dose group, the coughing rate after extubation in the 0.25 mg/kg group was 42.9%, and in the 0.5 mg/kg group was 23.3%, a difference of coughing rate between both groups of 19.6% (95% CI 3.17% to 36.03%, p-value for non-inferiority=0.998).

Conclusion: The treatment group (0.25 mg/kg of lidocaine) had less effective medicine than the control group (0.5 mg/kg of lidocaine) for preventing cough after extubation as well as the severity of cough.

Keywords: Fentanyl, Lidocaine, Cough, Post-operative sore throat, General anesthesia

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Although cough is a protective mechanism against aspiration, cough during tracheal extubation is common[1-3] and may be associated with undesirable complications like hypertension, tachycardia, laryngospasm, increase of intracranial pressure, intra-abdominal and intra-ocular pressure, and wound dehiscence[4-6]. Thus, effective cough suppression techniques have been developed to soften the emergence from anesthesia and prevent potential adverse effects such as deep extubation[7], no touch technique[8], and pharmacological interventions[9-12]. The effectiveness of intravenous lidocaine to shortly prevent extubation-induced cough has long been established with a dose ranging from 0.5 to 2 mg/kg with sparse adverse effects[13]. Despite the apparent safety profile of lidocaine, the medication is widely used with extra care due to reports of local anesthetic toxicity[14-16]. Sedation and delayed recovery of consciousness was also reported after systemic lidocaine administration to reduce cough[3,16] leading to the possibility of pulmonary aspiration of gastric contents after tracheal extubation. No study has investigated using 0.25 mg/kg lidocaine as an alternative technique to suppress post-extubation cough. Therefore, the objective of the present study was to compare the efficacy of cough suppression of 0.25 mg/kg to 0.5 mg/kg lidocaine administration before extubation.

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Materials and Methods

After receiving the Institutional Review Board of the Royal Thai Army Medical Ethics Committee approval, patients scheduled for elective surgery under general anesthesia at Phramongkutklao Hospital between December 2017 and June 2018, were enrolled and informed consent was obtained (TCTR 20180420005). Inclusion criteria comprised of being 18 to 60 years old. The present study enrolled 128 patients of the American Society of Anesthesiologists (ASA) physical status, I and II, and airway assessment of Mallampati classification I and II. Patients were excluded if they were unwilling to participate, had a history of allergy to local anesthetics, history of bronchial asthma, chronic obstructive pulmonary disease, respiratory tract infection, impaired kidney or liver function, or had been treated with angiotensin converting enzyme inhibitors or beta blocker. Other exclusion criteria included symptomatic bradycardia, tachyarrhythmia, left bundle branch block and second- and third-degree atrioventricular block, pregnancy, or language barrier.

All participants were randomized into two groups, blinded to their allocation using a computer-generated randomization table and concealed envelop. The control group (c-group) obtained 0.5 mg/kg, and the treatment group (t-group) received 0.25 mg/kg of lidocaine, two minutes before extubation.

An intravenous infusion of crystalloid solution was started since the patients had been admitted in the inpatient department. Mean arterial blood pressure (MAP), electrocardiography (ECG), peripheral pulse oximetry, and end tidal carbon dioxide ($ETCO_2$) were recorded upon arrival in the operating room (baseline), before induction, and every five minutes throughout the operation. In the operating room, pre-medication, induction, maintenance, and peri-operative analgesia were standardized and titrated intra-operative values depended on the anesthesiologist's adjustment in both groups. An anesthesiologist performed laryngoscopy in all groups using standard 3 or 4 Macintosh blades. Polyvinylchloride endotracheal tubes (ETTs) (Rüschelit; Rusch, Kernen, Germany) with an 8.0-mm ID for male and 7.5-mm ID for female were used for endotracheal intubation. No lubrication was applied on the ETT. The cuff was inflated with air to the point just capable of sealing leakage. Mechanical ventilation was initiated with O_2 in the air (FiO_2 0.4) with sevoflurane (1.5 to 2 vol%), keeping the end-tidal CO_2 between 32 and 35 mmHg. Supplemental doses of fentanyl and neuromuscular blockade were administered as required during anesthesia.

Intravenous ondansetron 0.1 mg/kg was administered, and residual neuromuscular blockade was reversed with intravenous atropine 0.02 mg/kg and prostigmine 0.05 mg/kg when the swallowing reflex was presented, followed by either 0.25 mg/kg or 0.5 mg/kg lidocaine administration two minutes before extubation. Gentle suctioning of oral secretions was conducted using a 12F soft suction catheter while limiting the suction pressure to 50 cmH_2O before tracheal extubation. After tracheal extubation, patients were transferred to the postanesthetic care unit. A standardized protocol was implemented for post-operative pain management and Mallampati classification, laryngoscopic view and operative time were recorded.

Data collected and recorded by the anesthesiologist blinded to group allocation included severity of cough immediately after extubation and post-operative sore throat (POST) at one hour after surgery, comprising of primary and secondary outcomes, respectively. Cough severity was graded on a 4-point scale (0=no coughing or straining; 1=moderate coughing; 2=marked coughing, straining; 3=poor extubation with laryngospasm)[17]. Sore throat was graded on a 4-point scale [0=no sore throat; 1=mild sore throat (less than the common cold); 2=moderate sore throat (similar to the common cold); 3=severe sore throat (more than the common cold)][18]. Adverse reaction that might occur after lidocaine administration was recorded.

The sample size calculation was based on non-inferiority trial. Savitha et al[19] reported post extubation cough suppression was 56.7% with 0.5 mg/kg of lidocaine and 26.7% with saline using non-inferiority margin of 0.01. Based on these results, 33 patients per group were required to achieve an alpha error of 0.05 and beta error of 0.2. Since the incidence of post extubation cough suppression from 0.25 mg/kg of lidocaine has never been reported, the authors increased the sample size up to 40 patients per group to ensure adequate sample size.

Statistical analysis was performed using SPSS, version 15 statistical software (IBM Corp., Armonk, NY). Categorical data were presented as percentages and continuous data were reported either as mean ± standard deviation (SD) (when normally distributed), or as median and interquartile range (IQR) (nonnormally distributed). The incidence of sore throat between groups was compared using chi-square or exact test and the significance level was considered a p-value less than 0.05. Non-inferiority test with margin of 10% and one-sided 95% confidence interval (CI) was performed by using R package.

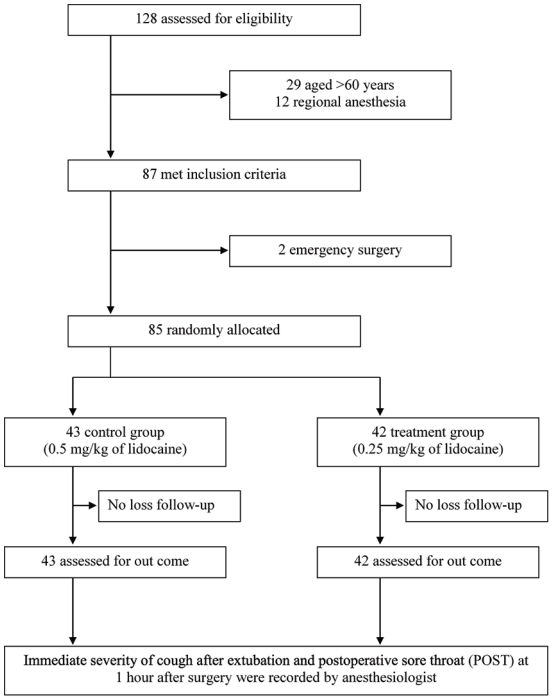

Figure 1. Enrollment, randomization.

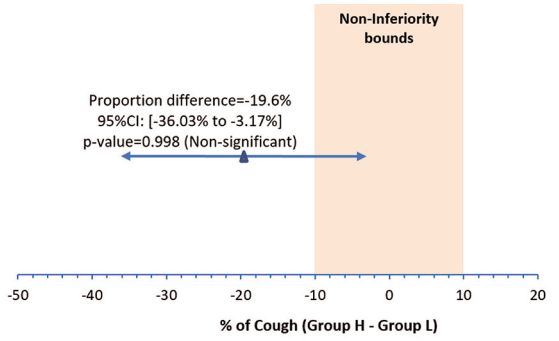

Figure 2. Percentage of patients who had extubated cough base on non-inferiority test with 10%margin.

Group H=0.5 mg/kg of lidocaine, Group L=0.25 mg/kg of lidocaine

Results

Eighty-five participants were enrolled in the present study as shown in Figure 1. Forty-two patients were assigned to the 0.25 mg per kg of lidocaine group (treatment) and 43 patients were assigned to the 0.5 mg per kg of lidocaine group (control). The baseline characteristics of the participants are presented in Table 1, and no significant difference was found between groups regarding gender, age, body mass index (BMI), underlying disease, operative type, Mallampati classification, laryngoscopic view, and operative time (p>0.05).

According to the non-inferiority margin in the present study of 10% compared with the high-dose group, the coughing rate after extubation in the 0.25 mg/kg group was 42.9%, and in the 0.5 mg/kg group was 23.3%, a difference of coughing rate between both groups of 19.6% (95% CI 3.17 to 36.03, p-value for non-inferiority=0.998) as shown in Figure 2. Therefore, the study group (0.25 mg/kg of lidocaine) had less effective medication than the control group (0.5 mg/kg of lidocaine) in preventing cough after extubation.

One of the 42 patients had severe cough, while four had moderate and 13 patients had mild cough in the 0.25 mg/kg lidocaine group. In the 0.5 mg/kg lidocaine group, two patients had moderate and eight patients had mild cough, as shown in Table 2. However, the study found that the 0.25 mg/kg group had more severity of sore throat than the 0.5 mg/kg group (p-value from Mann-Whitney U test=0.049; Cohen'd effect size=0.358).

Twenty-five patients in the 0.25% lidocaine (59.5%) and 24 patients in the 0.5% lidocaine groups (55.8%) had POST. No statistically significant difference was found between the two groups regarding overall incidence of sore throat (p=0.729). Three patients (7.1%) had moderate, and 22 patients (52.4%) had mild POST in the 0.25 mg/kg lidocaine group. Only one patient (2.3%) had severe, one patient (2.3%) had moderate and 22 patients (51.2%) had mild cough in the 0.5 mg/kg lidocaine group, without significant difference in severity of cough between groups (p=0.729) as shown in Table 3. Moreover, the control group was more likely to present reduced incidence of POST.

Discussion

The present study is the first randomized controlled trial comparing the efficacy of very low dose of 0.25 mg/kg to low dose of 0.5 mg/kg intravenous lidocaine to suppress cough. The present study revealed the control group did not significantly differ regarding the incidence and severity of cough and POST when compared with the treatment group, which correlated to related studies[13].

The incidence of cough in the control and the treatment groups were 42.9% and 23.3%, respectively, with p=0.055, which was just outside the level of significance. The small sample size might not be able to detect differences between the two groups. Thus, larger populations would be needed to confirm the

Table 1. Baseline characteristics

	0.25 mg/kg lidocaine (n=42) n (%)	0.5 mg/kg lidocaine (n=43) n (%)	p-value
Sex			0.902
Male	18 (42.9)	19 (44.2)	
Female	24 (57.1)	24 (55.8)	
Age, Mean±SD	41±11.4	42±12.4	0.699
Median (IQR)	40 (32, 54)	43 (32, 51)	
BMI, Mean±SD	24.34±4.2	24.43±4.5	0.618
HT			0.745
No	33 (78.6)	35 (81.4)	
Yes	9 (21.4)	8 (18.6)	
DM			0.676*
No	40 (95.2)	39 (90.7)	
Yes	2 (4.8)	4 (9.3)	
Operative type			0.282*
ENT	11 (26.2)	8 (18.6)	
Eye	2 (4.8)	8 (18.6)	
General surgery	7 (16.7)	8 (18.6)	
Gynecology	10 (23.8)	8 (18.6)	
Neurology	0 (0.0)	1 (2.3)	
Orthopedic	8 (19.0)	6 (14.0)	
Plastic	2 (4.8)	1 (4.6)	
Urology	2 (4.8)	2 (4.7)	
Mallampati classification			0.218*
1	26 (61.9)	31 (72.1)	
2	16 (38.1)	10 (23.3)	
3	0 (0.0)	1 (2.3)	
4	0 (0.0)	1 (2.3)	
Larygoscopic view			0.231*
Grade I	35 (83.3)	40 (93.0)	
Grade II	6 (14.3)	3 (7.0)	
Grade III	1 (2.4)	0 (0.0)	
Operative time, Median (IQR)	170 (128, 233)	165 (105, 210)	0.245

BMI=body mass index; HT=hypertension; DM=diabetes mellitus; SD=standard deviation; IQR=interquartile range

* Exact test

authors hypothesis.

Although randomization was used in the present study, the population ended up comprising adults, classified as ASA I or II. The authors further suggested conducting research focusing on patients classified as ASA III who constituted the vulnerable population. The study would be interesting for using very low dose lidocaine to suppress cough.

Post extubation sore throat is an unquestionably common adverse event. The present study confirmed the relatively high incidence of post extubation cough and sore throat, ranged from 33% to 57%; consistent with related studies[3,15,16,20]. Multiple factors such as operation time, ETT size, cuff shape and inflation pressure are all capable of inducing tracheal mucosal irritation and may lead to POST[21-24]. The present

Table 2. Number of patients who had extubated cough and severity of cough base on non-inferiority test with 10% margin

Time after extubation	0.25 mg/kg lidocaine (n=42) n (%)	0.5 mg/kg lidocaine (n=43) n (%)	p-value
No cough: 0	24 (57.1)	33 (76.7)	0.998
Cough	18 (42.9)	10 (23.3)	
1	13 (31.0)	8 (18.6)	
2	4 (9.5)	2 (4.7)	
3	1 (2.4)	0 (0.0)	

Table 3. Number of patients who had post operative sore throat

Sore throat	0.25 mg/kg lidocaine (n=42) n (%)	0.5 mg/kg lidocaine (n=43) n (%)	p-value
No: 0	17 (40.5)	19 (44.2)	0.729
Yes	25 (59.5)	24 (55.8)	
1	22 (52.4)	22 (51.2)	
2	3 (7.1)	1 (2.3)	
3	0 (0.0)	1 (2.3)	

study showed that the incidence of sore throat was not significantly different between the groups. The benefit of intravenous lidocaine was found in term of decreased incidence and severity of sore throat[25]. However, the use of topical lidocaine appeared of no benefit and even be worse in some cases[26-29]. These outcomes might have resulted from different anesthetic techniques, interviews, and the additives and preservatives in the solvent. These chemicals may have irritated the tracheal mucosa, potentially causing tracheal mucosa damage and increasing the severity of sore throat[28].

The exact mechanism of lidocaine injection to suppress cough and sore throat remains unclear. Several studies have reported that lidocaine significantly decreases in mucosal injury and inflammatory response due to inhibited ion exchange by the membrane channels themselves[30-32]. Direct central suppression and reducing the release of neuropeptides could occur[29].

The present study had several limitations. Firstly, although several different operations including ophthalmology, otolaryngology, and general surgery were included, to improve the generalizability of the present study, some otolaryngoscopic surgeries may be affected by the incidence and severity of post-operative cough and sore throat. Moreover, neurosurgery might lead to potential confounding factors but there was only one case of cranioplasty where the patient had full score of glasgow coma scale and ASA I classification. Additionally, patients undergoing non-airway surgery still need further evaluation. Secondly, the differences between the lidocaine and placebo groups were not recorded in the present study; therefore, the authors could not conclude that the effect of low dose lidocaine significantly differed from normal saline solution (NSS). However, a related study[19] summarized that lidocaine could significantly alleviate cough more than the saline group, i.e., 26.7% with saline. Thirdly, residual neuromuscular blockade was reversed when the swallowing reflex was presented. However, as neuromuscular monitoring was not applied in the present study, this might be a confounding factor.

Conclusion

Administering 0.25 mg/kg intravenous lidocaine has less effective in preventing the incidence and severity of cough and POST when compared to 0.5 mg/kg at the end of anesthesia.

What is already known on this topic?

Related studies have summarized that the action of lidocaine suppresses extubated cough and lowest dosage reported in related studies was 0.5 mg/kg(20). However, a dosage, lower than 0.5 mg/kg, has yet to be established.

What this study adds?

This study was the first randomized controlled trial of 0.25 mg/kg of lidocaine efficacy concerning extubated cough.

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Conflicts of interest

The authors declare no conflict of interest.

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