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The Effects of Intracuff Alkalinized Lidocaine on Patients Undergoing Uvulopalatopharyngoplasty and Prolonged Intranasal Intubation - *In Vitro* and *In Vivo* Pilot Study

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Abstract Endotracheal tube (ETT) frequently induces cough, hemodynamic response, postoperative sore throat, and hoarseness in patients with prolonged intubation. Intracuff alkalinized lidocaine (ICAL) is associated with reduced ETT related complications. This study investigated the effects of ICAL on obstructive sleep apnea (OSA) patients undergoing uvulopalatopharyngoplasty (UPPP) and prolonged intubation. In the *in vitro* study, we found that 5% sodium bicarbonate ($NaHCO_3$) dramatically increased lidocaine diffusion from the ETT cuff in 24 h, and the diffusion rate of lidocaine was correlated with the dose of alkalinized lidocaine in the ETT cuff. In the *in vivo* pilot study, we recruited 7 OSA patients undergoing UPPP with intranasal intubation under general anesthesia, among these patients, 4 EET cuffs were filled with air, and 3 were filled with 2% lidocaine and 5% $NaHCO_3$. All the patients were intubated overnight after surgery. We found that ICAL was ineffective to alleviate ETT induced agitation and cough at emergence from anesthesia. However, we found that ICAL significantly improved patients' sleep quality and satisfaction in the postoperative intubation period. The hemodynamic response was also well suppressed in patients with ICAL compared to those with intracuff air. In addition, ICAL improved the attending nurses' satisfaction that may reduce nurses' workload in the postoperative period. No adverse effects occurred. According to our study, we recommend using ICAL in patients with prolonged intubation, and further study is warranted.

Keywords: *intracuff, lidocaine, prolonged intubation*

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1. Introduction

Obstructive sleep apnea (OSA) is a common disorder of upper airway collapse during sleep, it may induce oxygen desaturation during sleep and may be associated with some systemic diseases such as hypertension, cognitive disorder, and metabolic disorder [1]. Therefore, alleviating upper airway obstruction for patients with OSA is of importance. Currently, one of the most effective treatments for OSA is to use a ventilator during sleep, yet to patients who are intolerant to ventilator, uvulopalatopharyngoplasty (UPPP) may be considered as another choice [2].

For OSA patients who undergo UPPP, postoperative inflammation, edema, and bleeding in the surgical field may induce acute upper airway obstruction. Therefore, patients with certain risk factors may need to be intubated for several hours or overnight [3]. However, patients with prolonged tracheal intubation could hardly tolerate the stimulation of the endotracheal tube (ETT) which lead to cough, hypertension, tachycardia, and even wound bleeding [4]. Therefore, alleviating the stimulation of ETT may help to decrease the incidence of postoperative complications in intubated patients after UPPP.

Intracuff lidocaine is to fill the ETT cuff with lidocaine that allows continuous diffusion of lidocaine from the cuff over the tracheal mucosa. Furthermore, adding sodium

bicarbonate ($NaHCO_3$) to lidocaine significantly increases the diffusion rate of lidocaine [5]. Clinical evidence showed that both intracuff lidocaine or intracuff alkalinized lidocaine (ICAL) significantly reduced the incidences of postoperative sore throat, coughing, agitation, hoarseness, and dysphagia in patients after general anesthesia with tracheal intubation [5,6].

Based on the benefits of ICAL, we hypothesized that ICAL may continuously alleviate the stimulation of ETT for OSA patients with prolonged intubation after UPPP. To the best of our knowledge, the relevant study is limited. This pilot study investigated the diffusion profile of lidocaine from the ETT cuff and the efficacy of ICAL in selected OSA patients with prolonged intubation.

2. Methods

2.1. *In vitro* Study

Nine polyvinylchloride (PVC) made high volume low pressure (HVLP) ID 6.5 cuffed ETTs (Well Lead Medical Co., Ltd., Guangzhou, China) were divided into three groups (n=3):

Group A: ETT cuff was filled with 2% lidocaine (lidocaine hydrochloride injection, Suicheng Pharmaceutical Co., Ltd., Zhengzhou, China) 6 ml (120mg).

Group B: ETT cuff was filled with 2% lidocaine 5 ml (100mg) and 5% $NaHCO_3$ (Sodium Bicarbonate Injection, Hebei Tiancheng Pharmaceutical Co. Ltd., Cangzhou, China) 1ml.

Group C: ETT cuff was filled with 2% lidocaine 4 ml (80mg) and 5% $NaHCO_3$ 2ml.

Every ETT cuff was immersed in 50 ml distilled water in a glass bottle. The bottles were put into a 37°C water bath for 24 h. Of every bottle, an aliquot of 500 μl distilled water around each ETT cuff was drawn at 7 time points (before ETT immersion, 1h, 2 h, 4 h, 8 h, 16 h, and 24 h after ETT immersion). The aliquots were stored in a refrigerator set at 4°C immediately after being drawn. After all of the aliquots were respectively collected, lidocaine concentration in each aliquot was detected using high performance liquid chromatography (HPLC).

For HPLC, a reversed phase C18 analytical column was used (Xtimate C18, 4.6 × 250 mm, 5 μm, Agilent 1260 Infinity HPLC, Agilent Technologies, Inc, USA). The mobile phase consisted with acetonitrile - phosphate buffer, pH 8.0 (50:50, v/v), flow rate 1.0ml/ml, 30°C. UV detection was carried out at 205 nm.

The lidocaine standard (Lignocaine base, LGC Ltd., UK) was diluted into 1 μg/ml, 10 μg/ml, 50 μg/ml, 100 μg/ml, and 500 μg/ml, these solutions were detected by HPLC to illustrate the curve of the relationship between lidocaine concentrations and peak retention areas.

2.2. *In vivo* Study

The pilot clinical study was approved by the Ethics Committee of Hunan Provincial People's Hospital (2020-26). 10 adult patients (aged 30-53 years, American Society of Anesthesiologists physical status II) with severe OSA scheduled for UPPP under general anesthesia with intranasal intubation, and anticipated to remain intubated after surgery were recruited. Exclusion criteria were allergy to lidocaine, uncontrolled cardiovascular disease, cardiac arrhythmia, tachycardia, respiratory disease (except for OSA), chronic cough, malformation of the upper airway, and cerebral disease. All the subjects had signed informed consents and were randomly allocated into two groups: Group Air and Group ICAL.

After arriving at the operating room, the patients were monitored by electrocardiogram, non-invasive blood pressure (BP), and pulse oximetry (SpO_2). Ringer's solution was infused at a rate of 4-6 mL/min via a peripheral intravenous line. Then dexmedetomidine was infused intravenously at a rate of 0.5 μg/kg/h, meanwhile, epinephrine (1: 2000000) and 2% lidocaine was used intranasally for nasal intubation. 15 min later, dexmedetomidine infusion rate was decreased to 0.2 μg/kg/h. The patients were preoxygenated by a fresh oxygen flow of 5-6 L/min through a facemask. Anesthesia was induced by sufentanil 0.4 μg/kg, cisatracurium 0.2 mg/kg, and propofol 1.5 to 2 mg/kg. A lubricated ID 6.5 PVC cuffed ETT was used for intranasal intubation, a video laryngoscope was inserted into the mouth to assist and confirm successful intubation.

Group Air: after intranasal intubation, the ETT cuff was inflated with air to obtain the minimal occlusive volume.

Group ICAL: after intranasal intubation, the ETT cuff was inflated with 2% lidocaine 4 ml (80 mg), then, 5% $NaHCO_3$ was injected immediately after lidocaine to the ETT cuff to obtain the minimal occlusive volume.

After the ETT was fixed, mechanical ventilation was initiated and was set to a fresh airflow of 2 L/min, inspired oxygen fraction 40%-60%, tidal volume 4-6 ml/kg, respiratory rate 12-15 breaths/min, and positive end expiratory pressure (PEEP) 5-6cmH_2O. Anesthesia was maintained with inhalation of 1.5%-2.5% sevoflurane, infusion of dexmedetomidine 0.2 μg/kg/h, and remifentanil 0.05-0.1 μg/kg/min. Sufentanil was administered in case of inadequate analgesia that was reflected by the vital signs. For every patient, methylprednisolone 1 mg/kg, flurbiprofen axetil 50 mg, and ondansetron 8 mg were administered intravenously for prevention of upper airway inflammation, postoperative pain, and postoperative nausea and vomiting (PONV), respectively.

After the operation was completed, sevoflurane and remifentanil were discontinued, the patients' lungs were flushed with fresh oxygen to facilitate emergence from anesthesia, dexmedetomidine was continuously infused at a rate of 0.2 μg/kg/h until extubation. The patients were transferred to post anesthesia care unit (PACU) after the emergence of anesthesia, every 5 μg of sufentanil was given intravenously if the patient was intolerant to the ETT after surgery. After an adequate evaluation, the patients were transferred back to the ward with nasal intubation and were monitored overnight without ventilator support until extubation.

The patients' perioperative mean arterial pressure (MAP), heart rate (HR), and SpO_2 were recorded at different time points: in the ward before surgery (T1), on arrival in the operation room (T2), emergence from anesthesia (T3), discharge from PACU (T4), on arrival in the ward (T5), and every 1h interval in the ward until extubation. The cough severity was graded as 0 (none), 1 (coughing once), 2 (coughing less than 5 s), 3 (coughing more than 5s or with head lifting) at emergence from anesthesia.

Sleep quality and ETT tolerance after UPPP were graded as 0 (poor), 1 (moderate), and 2 (good). The severity of postoperative sore throat and hoarseness after extubation were graded as 0 (no), 1 (mild), 2 (moderate), and 3 (severe). Patient and nurse satisfaction in the ward after surgery were graded from 0 (unsatisfactory) to 10 (very satisfactory).

The incidences of postoperative adverse events such as hypoxia (SpO_2 < 90%), PONV, active wound bleeding, and unintended extubation were also recorded.

2.3. Statistical Analysis

Statistical analysis was performed using GraphPad Prism 6 software (GraphPad Software, San Diego, CA, USA). Data were presented as mean ± standard deviation (SD), number, and percentage. Groups were compared using Student's *t*-test, χ^2 test, repeated-measures analysis of variance (ANOVA), or nonparametric test. Values of $p < 0.05$ were considered statistically significant.

3. Results and discussion

3.1. *In vitro* Study

As shown in Figure 1, the peak retention time of lidocaine standard was 13.792 min (arrowed). Figure 2 and Table 1 show the diffusion profile of lidocaine from the ETT cuff during 24 h. Previous studies have shown that both 8.4% and 1.4% $NaHCO_3$ significantly increased the diffusion rate of lidocaine from the ETT cuff [7]. 5% $NaHCO_3$ is the only commercially available concentration in China. The results showed that 5% $NaHCO_3$ also dramatically increased the diffusion rate of lidocaine from the ETT cuff ($p < 0.001$, Figure 2 and Table 1). In addition, from the 4th hour, the lidocaine diffusion rate in Group B was significantly higher than in Group C ($p < 0.001$, Figure 2 and Table 1), indicating that it may be the dosage of lidocaine but not the dosage of $NaHCO_3$ which mainly affected the diffusion rate of lidocaine. This was consistent with previous studies [5,7]. Besides, Figure 2 shows that the lidocaine diffused fast in the first 8 h in Group B and Group C, which indicates that the maximal local anesthetic effect of ICAL may be in the first 8 h after intubation. Meanwhile, this curve also indicates that after 8h of intubation, the diffusion rate of lidocaine decreased (Figure 2), which is also similar to a previous study [7]. This phenomenon may be due to decreased intracuff pressure [8], decreased dose of alkalinized lidocaine, and decreased concentration gradient between intracuff lidocaine and extracuff lidocaine. Therefore, we speculated that ICAL could continuously provide local anesthesia at least for 24 h, and the anesthetic effect may diminish after 8 h because of the decreased diffusion rate of ICAL.

3.2. *In vivo* Study

In our institution, severe OSA patients who are at risk of postoperative complications after UPPP are arranged to be intubated without ventilator support overnight. Therefore, alleviating their discomfort of being intubated during the postoperative period is of importance. In the pilot clinical study, we recruited 10 OSA patients, 3 patients were dropped due to being extubated in the PACU because of unnecessary to be intubated overnight judged by the surgeon during surgery. Hence 7 patients finally completed the study, 4 in Group Air and 3 in Group ICAL. All of the patients were extubated the next morning after surgery.

There were no significant differences between the two groups in the patients' characteristics and perioperative information (Table 2). A previous meta-analysis demonstrated that ICAL significantly reduced emergence cough and agitation [6], a randomized trial also showed that for surgeries with a duration of < 1 h, ICAL with a dose of 40 mg lidocaine significantly reduced emergence cough [9]. These results are inconsistent with our study. Our study showed that the duration of the surgeries was longer than 1 h (Table 2). In both of the two groups, the MAP and HR increased and the SpO_2 decreased at T3 compared to those at T1 (Figure 3, Figure 4, and Figure 5). Meanwhile, the increase of HR at T3 was greater in Group ICAL than in Group Air (Figure 4). These results indicated that the patients in both of the two groups agitated at emergence from anesthesia and ICAL failed to alleviate the agitation. In addition, Table 3 shows that all of the patients in both of the two groups severely coughed at emergence from anesthesia, indicating that ICAL also failed to suppress emergence cough after surgeries with a duration > 1h. The inefficacy of ICAL on emergence agitation and cough in our study is similar to that reported by D'Aragon et al. [10]. These inconsistencies of the effects of ICAL on patients during anesthesia emergence may be due to different study designs. However, since ICAL merely alleviates the stimulation from the ETT cuff, the stimulations on the nose, pharynx, vocal cords by ETT may induce emergence agitation and cough [11].

On the other hand, the MAP and HR in Group ICAL were relatively well suppressed at most of the time points in the postoperative period compared to Group Air ($p < 0.001$, Figure 3 and Figure 4). Meanwhile, patients' sleep quality and satisfaction in Group ICAL were significantly better than in Group Air ($p < 0.01$, Table 3). These results indicated that ICAL might continuously alleviate ETT stimulation and improve patients' comfort during the ETT retention period. A previous study showed that ICAL increased ETT tolerance and reduced analgesic requirements for mechanically ventilated patients in the first 24 h [12]. Our study demonstrated that ICAL may also be beneficial for patients with prolonged intranasal intubation without ventilator support. In addition, we investigated the satisfaction of the attending nurses in the postoperative period and found that ICAL also reduced their workload and hence improved their satisfaction ($p = 0.008$, Table 3). There were no significant differences regarding the severity of postoperative sore throat and hoarseness in the two groups, which was also inconsistent with previous studies [5,6,7,8]. We consider this inconsistency may be due to the inadequate sample size in our study. At last, there were no adverse events such as hypoxia, PONV, active wound bleeding, or unintended extubation occurred in both of the groups.

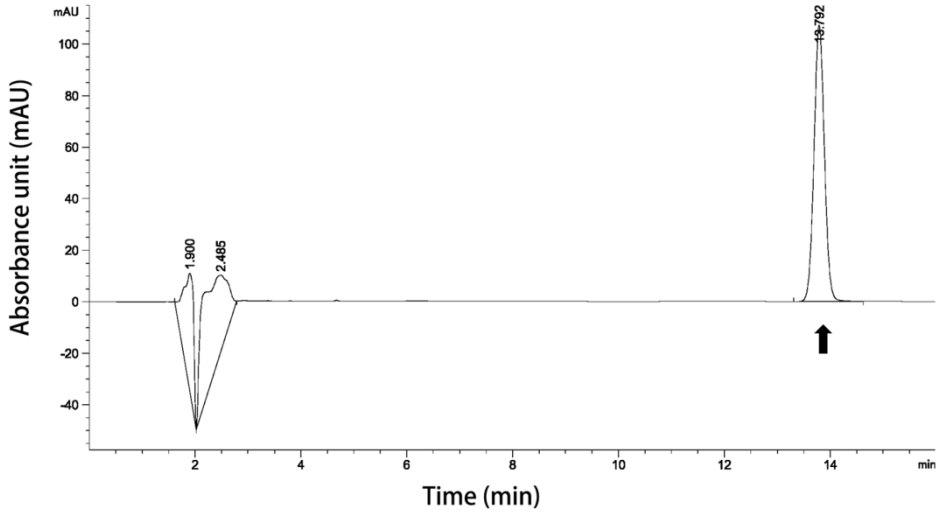

Figure 1. The retention peak of lidocaine standard (arrowed)

Table 1. The cumulative dose of lidocaine diffusion at different time points

Time (h)	Lidocaine diffusion dose (μg)		
	Group A	Group B	Group C
0	0±0	0±0	0±0
1	0±0	51.52±13.23	46.61±28.63
2	1.46±0.97	1802.81±423.89a	1402.28±297.49a
4	16.68±3.25	6994.79±849.06a	5778.81±724.80ab
8	56.49±4.34	20192.86±317.30a	17984.59±1020.08ab
16	139.65±5.77	27904.62±216.58a	25333.14±413.73ab
24	170.68±6.52	29502.04±197.07a	26665.09±416.88ab

a $p < 0.001$ compared with Group A at the same time point
b $p < 0.001$ compared with Group B at the same time point.

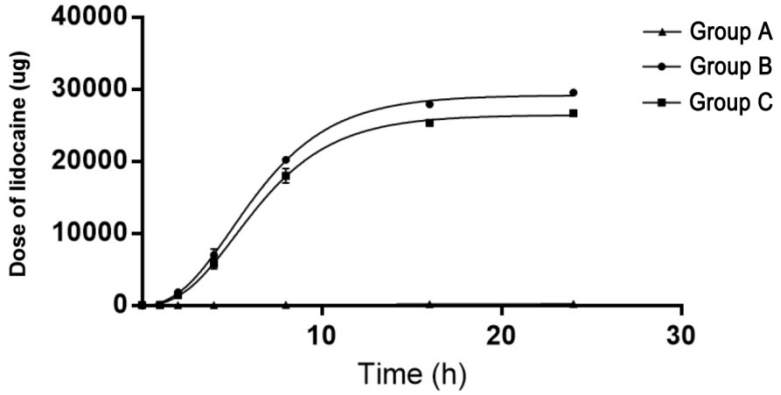

Figure 2. The curve of cumulative lidocaine diffusion dose as a function of time

Table 2. Patients characteristics and perioperative information

	Group Air	Group ICAL	*P* value
Gender (Male/Female)	4/0	3/0	/
Age (yr)	39±10	39±3	0.970
Weight (kg)	89.8±11.3	89.7±21.2	0.995
Height (cm)	172±5	171±4	0.911
BMI (kg/cm^2)	30.4±3.3	30.4±5.6	0.992
ASA status (I/II)	0/4	0/3	/
Intraoperative sufentanil dose (μg)	46±11	60±10	0.486
Operation time (min)	119±28	130±91	0.400
Emergence time (min)	9±3	7±3	0.361
Length of PACU stay (min)	53±29	46±26	0.771
Length of ETT retention after surgery (h)	15.1±1.9	14.7±3.1	0.816

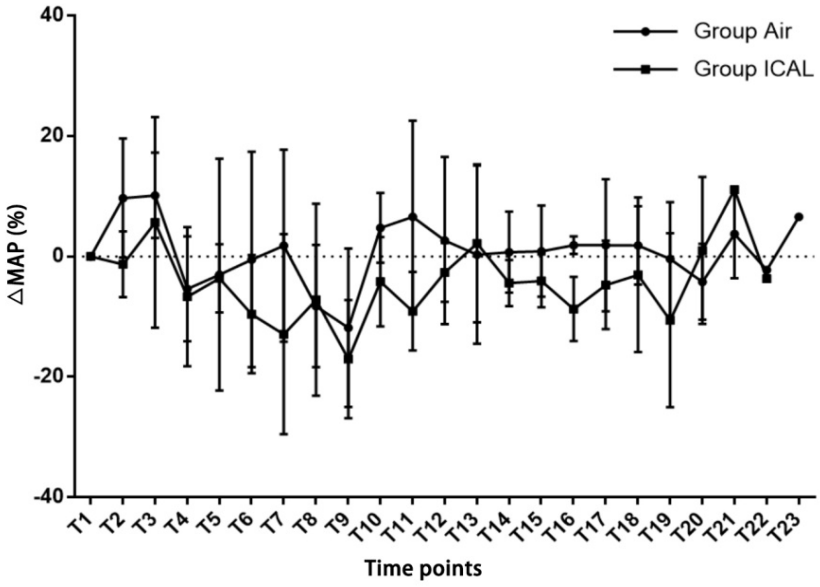

Figure 3. Perioperative MAP changes in the two groups expressed as percentage of basal value (△%MAP) (T1: in the ward before surgery. T2: on arrival in the operation room. T3: emergence from anesthesia. T4: discharge from the PACU. T5: on arrival in the ward. T6-T23: every 1 h after arrival in the ward.)

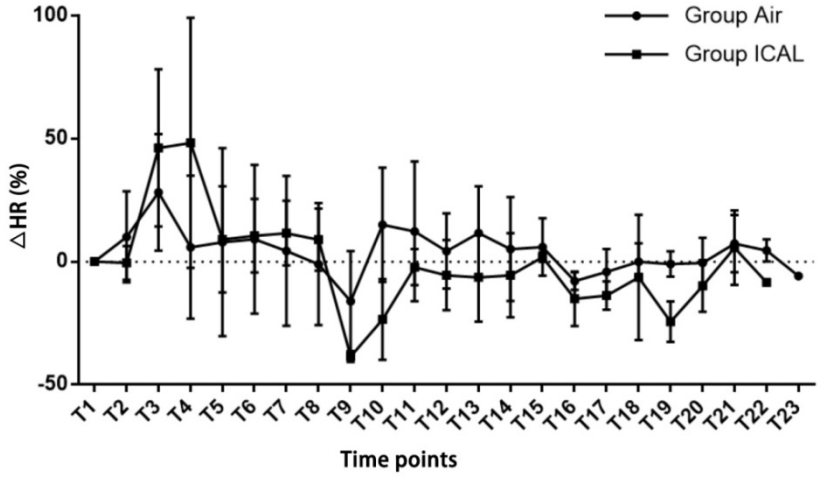

Figure 4. Perioperative HR changes in the two groups expressed as percentage of basal value (△%HR) (T1: in the ward before surgery. T2: on arrival in the operation room. T3: emergence from anesthesia. T4: discharge from the PACU. T5: on arrival in the ward. T6-T23: every 1 h after arrival in the ward.)

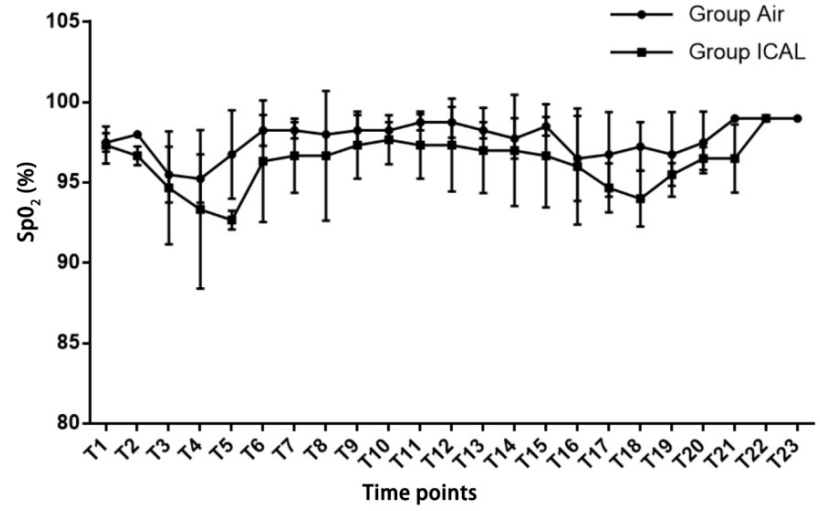

Figure 5. Perioperative SpO_2 changes in the two groups (T1: in the ward before surgery. T2: on arrival in the operation room. T3: emergence from anesthesia. T4: discharge from the PACU. T5: on arrival in the ward. T6-T23: every 1 h after arrival in the ward.)

Table 3. Results of patient and nurse responses and postoperative complications

	Group Air	Group ICAL	P value
Cough at emergence	3±0	3±0	/
Sleep quality	0.5±0.6	2±0a	0.007
ETT tolerance	1±0.8	1.7±0.6	0.286
Patient satisfaction	5.8±1	9.3±1.2a	0.006
Nurse satisfaction	6.5±0.6	9.3±1.2a	0.008
Postoperative sore throat	1.5±1	0.3±0.6	0.135
Postoperative hoarseness	0.5±0.6	0.3±0.6	0.721
Hypoxia, n (%)	0 (0)	0 (0)	/
PONV, n (%)	0 (0)	0 (0)	/
Active wound bleeding, n (%)	0 (0)	0 (0)	/
Unintended extubation, n (%)	0 (0)	0 (0)	/

a $p < 0.01$ compared with Group Air.

4. Limitations

There were some certain limitations in our study. First, the sample size in the clinical pilot study is small, a larger sample size may provide more convincible results. Second, the ETT cuffs in Group Air were filled with air not saline, which made the clinical study hard to be conducted with blind evaluation. Third, since the cough episodes were difficult to evaluate in the postoperative period, the study did not provide evidence of the effect of ICAL on cough in the postoperative period.

5. Conclusion

The *in vitro* and *in vivo* pilot study showed that the addition of 5% $NaHCO_3$ to intracuff lidocaine could dramatically increase lidocaine diffusion from the ETT cuff for 24 h. For patients undergoing UPPP and prolonged intranasal intubation, ICAL failed to alleviate agitation and cough at the emergence of anesthesia but effectively improved the ETT tolerance in the postoperative period.

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Yi Zou, Xiao Yan, and Yingzi Ling contributed equally to this work.

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