# Compound Lidocaine cream combined with tetracaine prevents cough reaction of patients with general anesthesia caused by extubation: a randomised controlled trial

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# Abstract

**Background:** Coughing response caused by tracheal extubation is the most common in general anesthesia patients with tracheal intubation during recovery from anesthesia. However, high aerosol production by coughing during recovery from general anesthesia in patients with respiratory infections (especially COVID-19) is one of the highest risk factors for infection among healthcare workers. Application of local anesthetics to the endotracheal tube is an effective method to reduce the choking reaction. The most commonly used anaesthetics are compound Lidocaine cream and tetracaine injection. However, there is still a certain number of choking reactions in the clinic when the two anaesthetics are used alone. We speculate that the combined application of compound Lidocaine cream and tetracaine will play a better role in prevent coughing response caused by tracheal extubation.

**Methods:** A total of 211 patients, who had undergone laparoscopic cholecystectomy or cholecystectomy combined with common bile duct exploration under general anesthesia, were randomly assigned to Group C (saline injection, 53 cases), Group L(compound lidocaine cream, 52 cases), Group T (tetracaine, 52 cases) and Group F (compound lidocaine cream combined tetracaine, 54 cases). Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), levels of epinephrine and levels of norepinephrine were recorded or measured immediately before extubation and one minute after extubation. In addition, endotracheal tube tolerance, the incidence of bucking, the incidence of agitation, the active extubation rate, the incidence of postoperative pharyngeal pain and the incidence of postoperative cough were analyzed.

**Results:** Blood pressure and heart rate as well as blood concentrations of epinephrine and norepinephrine were significantly higher in the group C compared with the every other group at the time of extubation as well as 1 min after extubation ($P < 0.001$). And group F significantly reduced the Blood pressure and heart rate as well as blood concentrations of epinephrine and norepinephrine compared group L or group T ($P < 0.05$, $P < 0.01$ or $P < 0.001$). When the patients emerged from general anesthesia, 96% of the group C had cough caused by sputum aspiration and extubation, which was significantly reduced by group L (61.5%, $P < 0.001$), group T (75%, $P < 0.05$) and group F (22.2%, $P < 0.001$), furthermore, group F significantly reduced the incidence of cough compared group L or group T ($P < 0.01$). Assessment of endotracheal tube tolerance, the score in the group C ((1, 3) 4, $P < 0.001$) is higher than group L ((0, 1) 2), group T ((0, 1.25) 3) and group F ((0, 0) 1), furthermore, group F significantly reduced the score compared group L or group T (P < 0.05, P < 0.01, respectively). The incidence of agitation and the active extubation rate were also higher in group C (96.2%, 71.7%, respectively, $P < 0.001$) than group L (48.1%, 15.4%, respectively), group T (61.5%, 26.9% respectively) and group F (17.3%, 7.7% respectively), furthermore group F significantly reduced the incidence of cough compared group L or group T (P < 0.05 or $P < 0.01$). In addition, the incidence of postoperative pharyngeal pain and the incidence of postoperative cough were no statistical difference between every group

**Conclusions:** Compound Lidocaine cream combined tetracaine may be a more advantageous approach for preventing choking and stabilizing circulation during extubation in emergence from general anesthesia, which may play an important role in preventing medical staff from contracting respiratory infectious diseases.

**Trial registration:** Chinese Clinical Trial Registry: ChiCTR2200058429 (registration date: 09-04-2020) “retrospectively registered”.

## Introduction

Coughing response caused by tracheal tube in general anesthesia is the most common in clinic medicine, especially when the tracheal tube is extubated, the incidence is between 38% and 96%[1]. Patients with respiratory infections (especially for COVID-19) generate a lot of aerosol by cough during recovery from general anesthesia, which is one of the highest risk factors for infection among medical staff [2–4]. Therefore, reducing the incidence of cough during recovery from general anesthesia is essential to reduce the risk of infection of medical staff with respiratory viruses. The irritation of the endotracheal tube to the epiglottis and airway mucosa is the anatomical cause of coughing and sore throat. Compound Lidocaine cream applying tracheal tube or tetracaine spraying on airway mucosa is the most commonly used method to prevent cough due to extubation from general anaesthesia [5, 6]. However, in our clinical anesthesia work, there are still nearly 50% of patients with choking and coughing reactions. Tetracaine has strong mucosal permeability and has a good effect on mucosal surface anesthesia [7], but tetracaine spraying on the airway surface is not very convenient in clinical application, especially for patients with respiratory infectious diseases. A mucoadhesion, thermal energy reversal hydrogel containing tetracaine for anesthesia in intranasal surgery with good anesthesia effect[8]. Therefore, we speculate that compound Lidocaine cream combined with tetracaine coating the surface of the endotracheal tube can reduce the coughing response during recovery from general anesthesia. The purpose of our study was to carry out an RCT trial on this application. The results offer accurate evidence for compound Lidocaine cream combined tetracaine coating the surface of the endotracheal tube can reduce the incidence of cough, and provide clinical experience for anesthesiologists and other medical personnel to protect themselves and improve the quality of care for patients during general anesthesia surgery during the COVID-19 epidemic.

## Methods

## Trial design

The RCT trial was organized by the The Affiliated Hospital of Yan’an University, China. The trial was conducted according to the CONSORT-2010 guidelines. The protocol of this study was approved by the Ethics Committee of The Affiliated Hospital of Yan’an University (NO. 2020042) and all subjects provided written informed consent before the trial by each participant or legal guardian.

## Participants And Setting

Patients were included in the trial if they were 18  64 years old and scheduled for Laparoscopic cholecystectomy or cholecystectomy combined with common bile duct exploration under general anesthesia using endotracheal tube intubation from March 2020 through December 2020. The major exclusion criteria were the following: difficult airway; allergies to lidocaine, tetracaine, or any other ingredients in the test product; intraoperative bronchospasm; preoperative chronic pharyngitis, cough and other upper respiratory tract lesions; patients with concurrent hypertension with or without drug therapy; operation time greater than 2.5 hours; intraoperative bleeding ( 300 ml); American Society of Anesthesiologists (ASA) Grade is over . We randomly assigned the patients to placebo (normal saline), compound lidocaine cream, tetracaine or compound Lidocaine cream combined tetracaine treatment at a 1:1:1:1 ratio. The primary end point included cardiovascular reactions during the extubation after anesthesia, along with endotracheal tube tolerance cough events during the recovery period and overall incidence of cough and sore throat within the first 24 h after extubation. Figure 1 shows a flowchart for the assignment of participants in the study.

# Randomization And Blinding

236 random numbers were generated by IBM SPSS Statistics 25, and the 236 numbers were randomly divided into four groups by the software. The enrolled cases were enrolled according to the order of enrollment time corresponding to random numbers from small to large, and a random number corresponds to the admission ID number of the patient. This part is undertaken by investigator A (one full-time staff with anesthesiologist qualification). The patient entered the operating room, investigator A induced general anesthesia according to the conventional method, and performed tracheal intubation after smearing and spraying the tracheal tube according to the enrollment information. After the tracheal intubation was completed, investigator B (an anesthesiologist participating in this research project) performed anesthesia management according to the conventional method, and was responsible for collecting data until the end of the study. All the collected data were handed over to the investigator A to sort out the data of different groups, and handed over to the investigator C for statistical analysis. The patients, investigators B, and C were all unaware of the grouping information.

# Intervention

The anesthesiologist **A** treated the surface of the tip of the endotracheal tube according to the random number table by predetermined medication or saline, normal saline(2 ml)in group C, 2 g compound lidocaine cream in group L, 10% tetracaine 2 ml in group T and compound lidocaine cream 2 g combined 10% tetracaine injection (2 ml) in group F. The compound lidocaine cream was applied and the tetracaine injection or the NS was sprayed on the surface of the tracheal tube cuff. The method of applying compound Lidocaine cream (compound lidocaine cream, 10g, containing 25mg each of lidocaine and prilocaine, Tongfang Pharmaceutical Group Co., Ltd. Beijing China) to the surface of the tracheal tube cuff is according to the previous study [5], The method of spraying tetracaine (tetracaine Hydrochloride for Injection, 50 mg, Chengdu Zhengkang Pharmaceutical Co., Ltd. Chengdu, China) to the surface of the tracheal tube cuff is according to the previous clinical experience of our department. Moreover, we modified lidocaine cream to compound lidocaine cream in the manuscrip. After ventilation, the anesthesiologists placed the endotracheal tube and fixed the endotracheal tube. Both the patients and the investigators were unaware of the trial-group assignments. Before tracheal intubation, anesthetics were used and unconscious intubation was carried out. The depth of anesthesia was measured by the bispectral index and the BIS was maintained 40 ~ 60 level. Sufentanil, propofol and rocuronium bromide were used as the induction agent according to the sex and weight of the patients. Rocuronium bromide acted as the muscle relaxant, remifentanil and propofol used according the weight and situation of the patients during the operation.

# Parameter Measurement

The primary outcome measure was the incidence of induced coughing reaction due to endotracheal extubation. The definition of induced cough: patients with coughing induced by sputum aspiration and extubation during recovery from anesthesia. Secondary outcome measures were the incidence of agitation, active extubation, postoperative cough and postoperative pharyngeal pain caused by extubation, the assessment of endotracheal tube tolerance and the assessment of cardiovascular reaction during the induction of extubation. The degree of endotracheal tube tolerance is defined as 0–5 points (no response during breath including spontaneous and mechanical ventilation condition, 0; no response during breath including spontaneous and mechanical ventilation condition, but slight action response to aspiration of sputum, 1; tolerance to mechanical ventilation, but medium action response to aspiration of sputum, 2; tolerance to ventilation, severe coughing reaction caused by sputum aspiration, 3; can not tolerate mechanical ventilation, severe coughing reaction caused by sputum aspiration 4; extubation behavior, 5). The degree of cough is defined as 0–3 points  No cough, 0; mild cough, 1; moderate cough, 2; severe cough, 3 . The definition of agitation: patients with agitation showed by thrashing to violent behaviour and removal of tubes and catheters during recovery from anesthesia according to previous reports [10]. The definition of active extubation: the patient has the behavior of pulling out the tracheal tube by hand, but it is not pulled out (we have special staff to take care of it, and we will not let it happen) during recovery from anesthesia. The definition of postoperative cough: spontaneous coughing more than 5 times and lasted longer than 5 s within the first 24 h after extubation, as the previous assessments described[9]. Cardiovascular reaction during the induction of extubation: systolic blood pressure (SBP) (mm Hg), diastolic blood pressure (DBP) (mm Hg), heart rate (HR) (beats/min), levels of epinephrine (E) (pmol/l) and levels of norepinephrine (NE) (pmol/l). The SBP, DBP, and HR were measured with a monitor. Blood samples were collected at immediately before extubation and one minute after extubation, from the arm that was not on intravenous infusion, according to previous reports [9]. Concentrations of blood hormones including epinephrine and norepinephrine were measured by ELISA using commercially available kit (IBL, Germany) and ELISA plate reader (BioTek, Winooski, VT, USA). The depth of anesthesia was assessed by BIS during general anesthesia.

# Sample Size Calculation

According to our previous pre-experiment, the incidence of cough response induced by extubation was 95% in the group C, 45% in the experimental group L, 60% in the experimental group T, and 15% in the experimental group F, we set $\alpha = 0.05$ and $\beta = 0.25$, with a sample drop rate of 15%. Using PASS 15, we calculated the minimum sample size of 59 cases in each group (a total of 236 cases).

## Statistical analysis

The measurements were calculated as the mean (± standard deviation). ANOVA was used to compare every different group. Nonparametric one-way ANOVA (Kruskal-Wallis test) was used for rating data. Further, the Pearson's chi-square test was used to compare the categorized data in the groups. We set $p < 0.05$ as statistically significant. SPSS 25 was used to process the data.

### Results

## Patients

A total of 236 patients at the Affiliated Hospital of Yan 'an University were enrolled in the randomized trial. And 24 patients were excluded from this study, 6 cases in group C (difficult airway: 2 cases; patients with concurrent hypertension: 3 cases), 7 cases in group L (difficult airway: 2 cases; preoperative chronic pharyngitis: 2 cases; allergies to compound Lidocaine cream: 1 cases; patients with concurrent hypertension: 2 cases), 7 cases in group T (difficult airway: 3 cases; allergies to compound Lidocaine cream: 1 cases; patients with concurrent hypertension: 2 cases; operation time greater than 2.5 hours: 1 cases), and 5 cases in group F (difficult airway: 1 cases; operation time greater than 2.5 hours: 1 cases; intraoperative bleeding  300 ml : 1 cases; patients with concurrent hypertension: 2 cases). The study starts on March 1, 2020 and ends on December 31, 2020. The endpoint of the study was to observe the incidence of cough within the first 24 hours after extubation. There were no significant differences in the baseline characteristics (such as age, weight, BMI, sex, operation time, anesthesia time and depth of anesthesia) of the patients between the every group (Table 1). Every group was anesthetized with general anesthesia by tracheal intubation. The depth of anaesthesia was maintained by all intravenous anesthesia performed by remifentanil, propofol and cisatracurium.

Table 1
Patient Characteristics

| | Group C | Group L | Group T | Group F | $F/\chi^2$ | $p$ |
|---|---|---|---|---|---|---|
| Age(year) | 41.11 ± 9.811 | 43.71 ± 9.831 | 41.00 ± 9.770 | 42.81 ± 7.690 | 1.063 | 0.366 |
| Weight(kg) | 65.58 ± 10.11 | 65.60 ± 9.091 | 67.54 ± 9.881 | 67.02 ± 8.313 | 0.595 | 0.619 |
| BMI | 23.96 ± 4.617 | 23.83 ± 3.966 | 24.58 ± 4.747 | 24.43 ± 3.754 | 0.372 | 0.773 |
| Sex (male n (%)) | 9(16.7%) | 14(26.9%) | 10(19.2%) | 11(20.4%) | 1.733 | 0.630 |
| Operation time (hours) | 52.17 ± 23.79 | 46.23 ± 20.83 | 45.77 ± 25.37 | 49.37 ± ± 25.62 | 0.815 | 0.487 |
| Anesthesia time (hours) | 67.17 ± 23.79 | 61.23 ± 20.83 | 60.77 ± 25.37 | 64.37 ± 25.62 | 0.815 | 0.487 |
| Depth of anaesthesia | 48.04 ± 3.287 | 47.90 ± 4.146 | 46.40 ± 3.403 | 46.96 ± 3.458 | 2.476 | 0.063 |

# Primary Outcomes

We first assessed cough response, catheter tolerance, and laryngeal discomfort complications after extubation. The incidence of induced coughing were significantly reduced in group L, group T and group F, compared with group C ($p < 0.001$, $p < 0.01$ and $p < 0.001$, receptively); however, the incidence of coughing were significantly higher in group L or group T, compared with group F ($p < 0.001$) (Table 2). The incidence of agitation were significantly reduced in group L, group T and group F, compared with group C ($p < 0.001$, receptively); however, the incidence of agitation were significantly higher in group L and group T, compared with group F ($p < 0.01$, $p < 0.001$, receptively) (Table 2). The active extubation rates were significantly reduced in group L, group T and group F, compared with group C ($p < 0.01$, $p < 0.05$, $p < 0.001$, receptively); however the active extubation rate was only significantly higher in group T, compared with group F ($p < 0.05$) (Table 2). We further assessed catheter tolerance, the scores were significantly improved in group L, group T and group F, compared with group C ($p < 0.001$, $p < 0.01$, $p < 0.001$, receptively); however, the scores of catheter tolerance were significantly higher in group L and group T, compared with group F ($p < 0.01$, $p < 0.001$, receptively) (Table 2). The incidence of postoperative cough were significantly reduced in group L, group T and group F, compared with group C ($p < 0.01$, $p < 0.05$, $p < 0.01$, receptively ) (Table 2); the incidence of postoperative pharyngeal pain were significantly reduced in group L, group T and group F, compared with group C ($p < 0.05$, $p < 0.05$, $p < 0.001$, receptively ) (Table 2), and only the incidence of postoperative pharyngeal pain in group F was further significantly lower than group T ($p < 0.05$) (Table 2). We also evaluated the effects of tracheal catheters on the cardiovascular system due to extubation and sputum aspiration. The SBP, DBP, HR, E and NE at the time of admission to PACU were assessed as the basic levels for evaluation. In each patient, the tracheal tube was removed after sputum aspiration to clear the airway, and the SBP, DBP, HR, E and NE were reassessed at one minute after extubation. The △SBP, △DBP, △HR, △E and △NE were calculated by the second levels (the level at one minute after extubation) minus the basic levels, and these indexes were used to evaluate the effect of different anesthesia methods on airway surface anesthesia. The basic levels of SBP, DBP, HR, E, and NE were no statistical difference between every group (Table 3). However, the levels of △SBP, △DBP, △HR, △E and △NE were significantly reduced in group L, group T and group F, compared with group C ($p < 0.001$, receptively). But the △SBP were significantly higher in group L and group T, compared with group F ( $p < 0.05$, $p < 0.001$, receptively) ; the △DBP were significantly higher in group L and group T, compared with group F ( $p < 0.001$, receptively) ; the △HR were significantly higher in group L and group T, compared with group F ( $p < 0.01$, $p < 0.001$, receptively) ;the △E and △NE were significantly higher in group L and group T, compared with group F ($p < 0.05$, $p < 0.01$, or $p < 0.001$) (Table 3).

Table 2
Comparison of cough events, catheter tolerance during recovery period and postoperative cough and postoperative pharyngeal pain after operation between groups

| | Group C | Group L | Group T | Group F | $\chi^2/k$ | *p* |
|---|---|---|---|---|---|---|
| **Incidence of induced coughing** | 51(96.2%) | 32(61.5%)$^{***###}$ | 39(75.0%)$^{**###}$ | 12(22.2%%)$^{***}$ | 71.581 | 0.001 |
| **Incidence of emergence agitation** | 51(96.2%) | 25(48.1%)$^{***##}$ | 32(61.5%)$^{***###}$ | 9(16.7%)$^{***}$ | 70.478 | 0.001 |
| **Active extubation rate** | 20(37.0%) | 8(15.4%)$^{**}$ | 14(26.9%)$^{*#}$ | 3(5.6%)$^{***}$ | 18.575 | 0.001 |
| **Catheter tolerance** | (1,3)4 | (0,1)2$^{***##}$ | (0,1.25)3$^{**\ ###}$ | (0,0)1$^{***}$ | 67.46 | 0.001 |
| **Incidence of postoperative cough** | 21(38.9%) | 7(13.5%)$^{**}$ | 11(21.2%)$^{*}$ | 7(13.0%)$^{**}$ | 14.482 | 0.002 |
| **Incidence of postoperative pharyngeal pain** | 26(48.1%) | 13(25.0%)$^{*}$ | 18(34.6%)$^{*#}$ | 9(16.7%)$^{***}$ | 14.751 | 0.002 |

Compared with group C, $^{*}P < 0.05$, $^{**}P < 0.001$, $^{***}P < 0.001$, Compared with group F, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$.

Table 3

Comparison of cardiovascular reaction and leverl of E and NE during recovery period between groups

| | Group C | Group L | Group T | Group F | $F$ | $p$ |
|---|---|---|---|---|---|---|
| **SBP** | 120.3 ± 10.91 | 120.1 ± 12.04 | 121.4 ± 10.71 | 122.2 ± 10.89 | 0.426 | 0.735 |
| **△SBP** | 36.97 ± 8.080 | 21.42 ± 9.811$^{***\#}$ | 24.12 ± 11.25$^{***\#\#\#}$ | 15.95 ± 6.483$^{***}$ | 51.85 | 0.001 |
| **DBP** | 72.04 ± 9.028 | 68.37 ± 11.03 | 69.94 ± 9.266 | 71.85 ± 7.072 | 1.881 | 0.134 |
| **△DBP** | 21.84 ± 5.077 | 12.40 ± 5.501$^{***\#\#\#}$ | 14.11 ± 6.510$^{***\#\#\#}$ | 9.752 ± 5.234$^{***}$ | 45.79 | 0.001 |
| **HR** | 76.57 ± 5.869 | 75.23 ± 6.258 | 73.69 ± 6.958 | 74.28 ± 6.606 | 2.006 | 0.114 |
| **△HR** | 24.27 ± 4.833 | 14.84 ± 7.102$^{***\#\#}$ | 16.60 ± 8.126$^{***\#\#\#}$ | 10.04 ± 8.639$^{***}$ | 34.94 | 0.001 |
| **E** | 612.5 ± 39.86 | 600.3 ± 46.33 | 605.0 ± 54.77 | 618.1 ± 55.70 | 1.348 | 0.260 |
| **△E** | 730.0 ± 282.4 | 390.2 ± 306.8$^{***\#\#}$ | 463.4 ± 259.3$^{***\#\#\#}$ | 210.7 ± 277.1$^{***}$ | 31.23 | 0.001 |
| **NE** | 891.2 ± 228.6 | 923.5 ± 258.7 | 880.0 ± 251.7 | 948.2 ± 260.3 | 0.8174 | 0.486 |
| **△NE** | 1526 ± 326.6 | 726.4 ± 326.6$^{***\#}$ | 884.3 ± 326.6$^{***\#\#}$ | 313.1 ± 326.6$^{***}$ | 20.57 | 0.001 |

△NE:The level of NE 1 min after extubation minus the base value; compared with group C, $^{***}P<0.001$,;compared with group F, $^{\#}P<0.05$, $^{\#\#}P<0.01$, $^{\#\#\#}P<0.001$

# Discussion

In the current study, we demonstrated that compound Lidocaine cream or tetracaine injection or compound Lidocaine cream combined tetracaine was applied to the surface of the tracheal tube could significantly reduce the incidence of induced coughing, agitation caused by sputum aspiration and extubation and active extubation rate, significantly improved tolerance to the tracheal tube in patients with tracheal intubation under general anesthesia during anesthesia recovery. But there were at least 48.1% ~ 75.0% patients take place induced coughing and agitation in group compound Lidocaine cream and group tetracaine injection. However, the incidence of induced coughing and agitation were significantly reduced to 16.7% ~ 22.2% by compound Lidocaine cream combined tetracaine. Especially, the active extubation rate was also significantly reduced to 5.6% in group compound Lidocaine cream combined tetracaine. Compound Lidocaine cream combined tetracaine was performed the best effect in improving tolerance to tracheal tube in patients with general anesthesia. We further found that compound Lidocaine cream combined tetracaine is the most effective in preventing extubation induced blood pressure (both SBP and DBP), HR, E and NE level increased effect on the patients who emerged from general anesthesia. These findings suggested that compound Lidocaine cream combined tetracaine could perform the better effect of airway surface anesthesia and significantly increased tolerance to the catheter in patients with tracheal intubation under general anesthesia, and further reduce the release of the E and NE stabilizing hemodynamics.

Endotracheal intubation-related mechanical stimulation is clinically common and associated with various airway complications, such as severe coughing, laryngeal injury and postoperative sore throat [11, 12]. And coughing of patients with lung disease can produce large amounts of aerosols containing viruses and pathogenic microorganisms, such as patients with mycobacterium tuberculosis infection[13, 14], pseudomonas aeruginosa infection[15], and especially COVID-19 infection [16]. These aerosols containing viruses and pathogenic microorganisms can cause the spread of respiratory diseases. Therefore, it is very important to prevent the choking reaction caused by the endotracheal tube. Furthermore, the endotracheal tube induced airway response (especially during endotracheal intubation and extubation) is prone to increase the risk of adverse cardiovascular events including arrhythmias, hypertension, myocardial ischemia, and intracranial pressure elevation [17–19]. During the recovery period of general anesthesia, sputum aspiration and tracheal tube extraction are the strongest stimulation to tracheal mucosa and most likely to induce cough reaction. So far, the consensus among anesthesiologists is that compound Lidocaine cream can reduce the cough response caused by tracheal tube removal after general anesthesia. One study showed that compound Lidocaine cream significantly reduced the incident of cough caused by endotracheal extubation to 6.4% in old patients [5]. Our study showed that the compound Lidocaine cream also can significantly reduce the incident of cough caused by endotracheal extubation about 35% compared NS control group, but there are still 61% patients who have a cough response, perhaps this is because younger patients were more responsive to tracheal tube stimulation of the airway mucosa than older patients[20]. A review study also showed that local anesthetics did not attenuate cough associated with extubation [21], but another eta-study showed that topical airway anesthesia demonstrated better than placebo or no medication in reducing immediate post-extubation cough/bucking [22]. It is well known that tetracaine has a very strong mucosal penetration and can play a better mucosal surface anesthesia [7]. So we applyed compound Lidocaine cream to the tracheal tube and then sprayed 10% tetracaine 2 ml on top of lidocaine cream, which was performed to general anesthesia for tracheal intubation. Our study showed that compound Lidocaine cream combined tetracaine further significantly reduced the incidence of induced coughing caused by sputum suction and extubation about 39% compared only used by lidocaine cream. Although spraying tetracaine alone also significantly reduced the incidence of cough reaction caused by sputum suction and extubation, the cough reaction was the lowest in lidocaine combined with tetracaine. Therefore, compound Lidocaine cream combined with tetracaine can exert more satisfactory mucosal surface anesthesia effect. Another study on the combination of compound Lidocaine cream and tetracaine gel for vascular puncture showed that the combination of the two kind anesthetics increased the effect of anesthesia and shortened the time to onset [23], this study also supports our findings. Furthermore, spraying tetracaine on top of compound Lidocaine cream has more tetracaine local anaesthetic attached to the endotracheal tube than directly spraying tetracaine, which can exert anesthesia blocking effect. This was validated by the lower incidence of induced coughing reactions in the compound Lidocaine cream combined with tetracaine (22.2%) group compared the group tetracaine (75.0%). We know that the effect of surface anesthesia on the airway mucosa exerted by local anesthetics inhibits the airway reflexes caused by the tracheal tube and enhances the body's tolerance to the tube. In this study, we assessed the tolerability of endotracheal catheters. Our results show that compound Lidocaine cream or tetracaine significantly increased catheter tolerance, the catheter tolerance score was reduce to (0, 1)2 and (0, 1.25)3 respectively. Furthermore, compound Lidocaine cream combined tetracaine further significantly increased catheter tolerance, the catheter tolerance score was reduce to (0, 0)1. During recovery from general anesthesia, the patient presents emergence agitation due to poor tolerance from tracheal tube [24]. In our study, we found that compound Lidocaine cream or tetracaine significantly reduced the incidence of emergence agitation about 21% ~ 35% compered NS, and compered compound Lidocaine cream or tetracaine, compound Lidocaine cream combined tetracaine further significantly reduced the incidence of emergence agitation to 16.7% reduced about 30% ~ 40%. Other studies have shown that the incidence of emergence agitation has been much higher, ranging from 4.7% [10] to 19% [25]. Not surprisingly, postoperative recovery for agitated patients was more complicated, the reasons include discomfort from tracheal tube, urinary catheter or insufficient analgesia and so on. The most serious is the voluntary removal of the endotracheal tube during recovery in general anesthesia patients with endotracheal intubation. In our study, we found that compound Lidocaine cream or tetracaine significantly reduced the active extubation rate to 15% ~ 26%, and compound Lidocaine cream combined tetracaine significantly reduced the incidence of active extubation rate to 5.6%, compered NS (37.0%). Although compound Lidocaine cream (15.4%) compared compound Lidocaine cream combined tetracaine (5.6%) has no statistical significant in assessment of active extubation rate, the compound Lidocaine cream is twice higher than compound Lidocaine cream combined tetracaine.

These above findings may lead to beneficial effects on cardiovascular reactions in the course of endotracheal extubation. In the current study, we found that hemodynamic changes (blood pressure and / or heart rate) that exceeded at least 20% of the baseline after 1 min extubation. Compound Lidocaine cream or tetracaine significantly reduced the SBP increased from baseline (△SBP), the DBP increased from baseline (△DBP) and the HR increased from baseline (△HR), and the average value of △SBP, △DBP and △HR were reduced about 12 ~ 15 mmHg, 7 ~ 9 mmHg and 8 ~ 10 beat/min, respectively. And compound Lidocaine cream combined tetracaine further significantly reduced the average value of △SBP, △DBP and △HR, the average value of △SBP, △DBP and △HR were reduced about 10 mmHg, 6 mmHg and 4 beat/min, respectively, compared only using compound Lidocaine cream or tetracaine. The results of Mohammadali Attari, et al using laboratoryol [26] and Guoliang Zhao, et al. using remifentanil [18] to inhibit the increase in blood pressure caused by extubation are similar to ours. When the endotracheal tube is extubated, the tube stimulates the receptors of the airway mucosa, resulting in the release of a large number of catecholamines into the blood [27, 28], and the blood pressure and heart rate will inevitably increase. We found that catecholamines (E and NE) changes after 1 min extubation exceeded 1.1 to 1.7 times baseline in control group. However, compound Lidocaine cream or tetracaine significantly reduced the E and NE increased level from baseline (△E and △NE), and the average value of △E and △NE were reduced about 50%. And compound Lidocaine cream combined tetracaine further significantly reduced the average value of △E and △NE, the average value of △E and △NE were reduced about at least 50%, respectively, compared only using compound Lidocaine cream or tetracaine. Therefore, we demonstrated that compound Lidocaine cream combined tetracaine significantly suppressed blood levels of epinephrine, and norepinephrine at extubation, suggesting compound Lidocaine cream combined tetracaine might stabilize heart rate and blood pressure through preventing aforementioned hormones from increasing in response to uncomfortable stimulation such as endotracheal extubation. These results may be useful in preventing cardiovascular events during emergence from general anesthesia. Finally, we assessed the incidence of postoperative cough and postoperative pharyngeal pain. We found that using local anaesthetic significantly reduced these incidences compared using NS. The incidence of postoperative cough in lidocaine cream, tetracaine and compound Lidocaine cream combined tetracaine were no statistic difference compared each other. The result of assessing the incidence of postoperative pharyngeal pain was the same as assessing the incidence of postoperative cough, only the incidence of postoperative pharyngeal pain was higher in tetracaine than compound Lidocaine cream combined tetracaine. A study showed that Using lidocaine to inflate the endotracheal tube cuff at the end of surgery decreases the frequency of postoperative cough and sore throat [29], which is related to the good anesthetic effect of lidocaine on airway mucosal surface. The result also supports our research. We speculate that compound lidocaine cream combined with tetracaine applied to the surface of the tracheal tube not only prevents the choking caused by extubation in patients undergoing laparoscopic cholecystectomy and cholecystectomy combined with biliary exploration, but may also reduce the risk of choking in other patients with tracheal intubation. Extubation causes choking reaction, etc.

However, there were several limitations in the current study. First, our research is a single-center study, and later higher-level and complete research requires multi-center research. Second, this study did not observe the duration of the continuous effect of compound lidocaine combined with tetracaine on airway topical anesthesia. Third, whether compound lidocaine cream combined with tetracaine still plays a role in preventing extubation-induced coughing in patients with difficult airways requires further study.

# Conclusion

Our study revealed that smearing compound Lidocaine cream or spraying tetracaine on the tracheal tube can inhibit the coughing reaction caused by sputum suction or tracheal tube removal during recovery from general anesthesia, increase the body's tolerance to the tracheal tube, prevent the occurrence of active extubation, and reduce the release of catecholamine hormones into the blood and increase in blood pressure during extubation. More importantly, the combined application of compound Lidocaine cream and tetracaine can further significantly reduce the incidence of coughing reaction during recovery, and further significantly increase the tolerance of the catheter, further significantly inhibit extubation-induced increases in blood pressure and catecholamine levels, compared compound Lidocaine cream or tetracaine using alone. Therefore, compound Lidocaine cream combined tetracaine may be a more advantageous approach for preventing coughing and stabilizing circulation during extubation in emergence from general anesthesia, which may play an important role in preventing medical staff from contracting respiratory infectious diseases. Especially during the COVID-19 epidemic, there are significant clinical implications for anesthesiologists and other medical staff to provide clinical experience to protect themselves and improve the quality of care for patients undergoing general anesthesia procedures.

# Declarations

### Ethics approval and consent to participate

The protocol of this study was approved by the Ethics Committee of The Affiliated Hospital of Yan'an University (NO. 2020042) and all subjects provided written informed consent before the trial by each participant or legal guardian.

### Consent for publication

Not applicable.

### Availability of data and materials

The data-base used and /or analyzed during the current study and the full trial protocol are available from the corresponding author (Prof. *Erfei Zhang*, Department of Anesthesiology, The Affiliated Hospital of Yan'an University, Yan'an 716000, Shaanxi Province, P. R. China).

Tel: + 86 0911 2881264, e-mail: zhangerfei09@126.com) on reasonable request

### Competing interests

The authors declare that they have no competing interests.


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### Authors' contributions

Jie gao was responsible for the recruitment, randomization and tracheal tube anesthetic. Hailiang Zhang, Ying li, Lei Zhang, Taiyang Li and Min Wang performed anesthesia management and data collection. Erfei zhang, Xiaoying Zhao and Ting Li analyzed data and wrote manuscript. Erfei zhang reviewed/edited manuscript. The author(s) read and approved the final manuscript.


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# Figures

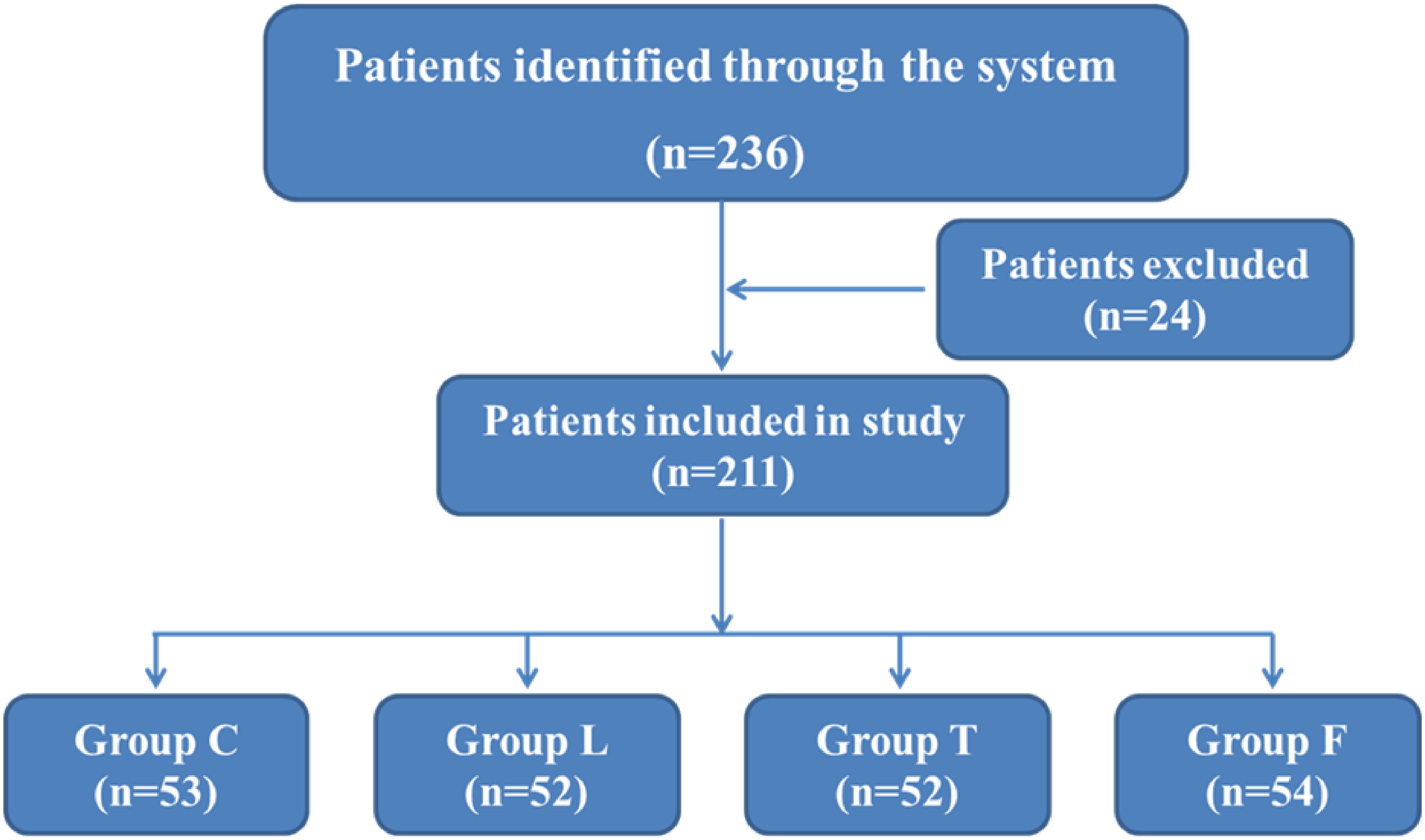


**Figure 1**

A total of 236 patients were included in the study according to the inclusion criteria of the trial design. Among them, 24 patients were excluded according to the exclusion criteria. A total of 211 patients were enrolled into the study and randomly divided into 4 groups, 53 patients in group C, 52 patients in group L, 52 patients in group T and 54 patients in group F.