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CLINICAL TRIAL REPORT

The Effect of Intravenous Lidocaine on EC50 of Remifentanil for Preventing Cough During Emergence in Female for Thyroid Surgery Anesthesia

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Objective: To evaluate the effect of intravenous lidocaine injection on the half-maximum effective concentration (EC50) of remifentanil in preventing cough due to tracheal extubation in female patients undergoing thyroid surgery by Dixon's sequential method.

Methods: A total of 50 female patients underwent elective thyroidectomy were randomly divided into two groups of a 1:1 ratio. Group L (lidocaine group) was given intravenous lidocaine (1.5 mg/kg) and then continuous infusion (2 mg/kg/h) until the end of surgery. Group C (control group) received 0.9% sodium chloride solution infusion in the same way. The primary outcome was effective concentration EC50 of remifentanil in preventing cough due to tracheal extubation in female patients undergoing thyroid surgery. The secondary outcomes were as follows: mean arterial pressure (MAP), oxygen saturation (SpO_2), heart rate (HR), $PetCO_2$ and respiratory rate at the time of tracheal extubation. The incidence of postoperative nausea and vomiting, and symptoms associated with lidocaine toxicity.

Results: Finally, 44 subjects completed the study. The EC50 values of remifentanil calculated using probit regression were 1.40 ng/mL (95% CI, 1.15–1.65 ng/mL) in Group C and 0.83 ng/mL (95% CI, 0.58–1.08 ng/mL) in Group L. A lower concentration of remifentanil can inhibit the cough reaction during intravenous lidocaine infusion. $PetCO_2$ in the lidocaine group was lower than that in the control group ($Z=-2.162$, $P < 0.05$). The respiratory rate of the lidocaine group after extubation was higher than that of the control group ($Z=-3.287$, $P < 0.05$).

Conclusion: Intravenous injection of lidocaine can reduce the effective concentration EC50 of remifentanil in preventing tracheal extubation cough in female patients undergoing thyroid surgery.

Keywords: lidocaine, thyroid surgery, remifentanil, extubation cough

Introduction

A majority of patients underwent general anesthesia were intubated through the endotracheal tube. An airway is protected from aspiration by coughing, which removes foreign objects from the airway. It is estimated that 15–94% of patients will cough after tracheal catheter removal during the recovery period of general anesthesia.[1] Cough may cause a range of adverse reactions, including laryngeal spasm, hypertension, tachycardia, intracranial hypertension, increased intraocular and intraabdominal pressure, and myocardial ischemia.[2,3] In patients undergoing thyroid surgery, it is crucial to prevent postoperative cough. A severe cough may result in wound cracking and hematoma formation.

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Many interventions have been proposed to reduce the incidence of coughing during tracheal extubation, including extubation under deep anesthesia, infusion of remifentanil, infusion of dexmedetomidine, and intravenous infusion of lidocaine.[4–6] As an ultrashort opioid receptor agonist, which acts on μ opioid receptor, remifentanil does not rely on kidney and liver metabolism. Previous studies have confirmed that continuous intravenous infusion of a certain dose of remifentanil during extubation can significantly reduce the cough reaction and hemodynamic abnormalities caused by extubation.[7]

As different types of surgery require different doses of remifentanil for cough suppression, the dose at which patients need to use remifentanil for cough suppression should be tailored accordingly.[8,9] Compared with traditional infusion, Target-controlled infusion can provide a more accurate and stable blood concentration of the drug for suppression of coughing.[2] However, in order to achieve an effective antitussive dose, continuous infusion of large doses of remifentanil during extubation has shortcomings such as respiratory depression, delayed recovery, and nausea and vomiting after extubation. In addition, the use of large doses of opioids can also activate neurons, which can lead to hyperalgesia and chronic postoperative pain.

Lidocaine, as a widely used local anesthetic, has analgesic, antialgic and anti-inflammatory properties. Recent studies have shown that perioperative intravenous infusion of lidocaine can not only reduce postoperative pain, accelerate postoperative recovery and weaken pharyngeal reflex.[10,11] Lidocaine is a relatively safe medication, if used in low doses. An infusion of no more than 3 $mg \cdot kg^{-1} \cdot h^{-1}$ is safe.[12] Therefore, this study considered whether the combined application of intravenous lidocaine and remifentanil could reduce the EC50 value of remifentanil in inhibiting extubation cough while ensuring the effect of inhibiting extubation cough, so as to reduce the side effects of high-dose remifentanil infusion.

Methods

Study Design

The study was implemented in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of The First Affiliated Hospital of Fujian Medical University (Number.2021–197). Written informed consent was obtained from all participants. This study was registered with the Chinese Clinical Trial Registry (ChiCTR) (www.chictr.org) (registration ID: ChiCTR2100051897). The study execute time is from October 2021 to June 2022.

Fifty female patients undergoing thyroidectomy were enrolled in the study. The inclusion criteria were: (1) 18–65 years old women; (2) perform thyroidectomy under general anesthesia with tracheal intubation; (3) categorized as Anesthesiologists physical status classification of American Society I ~ II (ASA I ~ II); and (4) agree to engage in our study and sign the informed consent. The exclusion criteria were: (1) hypersensitivity to any of the study drugs or excipients; (2) have a history of opioid analgesics, sedative hypnotics and alcohol abuse; (3) patients with severe heart, liver, brain, lung, and kidney diseases; (4) patients with smoking, asthma, sarcoidosis, interstitial lung disease, or other respiratory diseases; (5) the body mass index (BMI) $\geq$ 30 kg/m^2.

The enrolled patients were allocated into lidocaine group (Group L: A load dose of lidocaine (1.5 mg/kg) was administered intravenously, followed by a continuous infusion (2 mg/kg/h) until the end of surgery) or control group (Group C: The same amount of 0.9% NaCl solution was injected in the same manner) using the random number table method. The group allocation was done by a researcher, who was not involved in data collection and patient management. Participants in the study and investigators who assessed the outcomes were blinded to any details about the groups.

Anesthetic Procedure

All subjects had a standard anesthesia technique, including sufficient preoxygenation of 3 min before anesthesia. Standard monitoring was applied, and general anesthesia was induced with sufentanil (0.3 ~ 0.4μg/kg), atracurium (0.15 mg/kg), and propofol (1.5 ~ 2.5mg/kg). After tracheal intubation, anesthesia was maintained with target-controlled infusion of remifentanil (2 ~ 5ng/mL) and sevoflurane in a mixture of 40% air and 60% O_2 to keep the heart rate and blood pressure. Hypotension (systolic blood pressure < 80mmHg) was treated with 5μg of norepinephrine and

bradycardia was treated with 0.5mg of atropine (HR < 45 beats/min). Subjects were extubated in the operating room after surgery.

Remifentanil was adjusted to a pre-determined level (eg, 2 ng/mL for the first patient) prior to wound suturing and continued for at least 15 minutes until tracheal extubation to ensure stable plasma and site of action concentrations (moderate or severe cough during extubation means positive extubation cough, remifentanil effect point concentration was increased by 0.2ng/mL in the next patient. If a negative extubation cough reaction occurs, the effect point concentration of remifentanil can be reduced by 0.2ng/mL. At the end of the procedure, sevoflurane was discontinued, 100% oxygen flow was adjusted to 6L/min, and all patients received flurbiphenolate (1mg/kg) for analgesia and tropisetron (5mg) to prevent vomiting. Until the patient receives instructions to open their eyes, manual ventilation replaces mechanical ventilation and requires the patient to breathe deeply. Extubation is performed when adequate spontaneous respiratory rate and tidal volume are confirmed and when oxygen saturation (SpO_2) is ≥ 95%. After extubation, discontinue remifentanil and give oxygen through the mask for 3 minutes. When the patient has reached a stable state, they are transferred to the post-anesthesia Care Unit (PACU) and monitored according to the institutional PACU protocol.

Outcome Measures

Coughing severity was measured using modified Minogue scale,[13] ranging from 0–3 as follows: 0, No cough; 1, Mild cough, only once without agitation; 2, Moderate cough, > once, but lasting <5s, restlessness but not affecting extubation; 3, Continuous cough > 5 s with head up and breath holding. The mean arterial pressure (MAP), oxygen saturation (SpO_2), heart rate (HR), $PetCO_2$ and respiratory rate were recorded at the time of entry (T0), 15 min before extubation (T1), tracheal extubation (T2), 1min after extubation (T3) and 5 min after extubation (T4). All of the patients were monitored for the symptoms or signs (arrhythmia, perioral numbness, visual disturbance and dizziness) associated with lidocaine toxicity during the perioperative period.

Adverse Reactions

It was defined as respiratory depression when SpO_2 was below 90% when inhaled oxygen or respiratory rate was below 10 breaths per minute. Respiratory depression and respiratory amnesia were recorded after extubation and before leaving the anesthesia recovery room. Hypotension was defined as a fall of systolic blood pressure below 80 mmHg.[14] Bradycardia is defined as a heart rate below 60 beats per minute,[15] and 0.5mg atropine is required if it is less than 45 beats per minute. Itching, nausea, and vomiting were also assessed.

Statistical Analysis

Studies have shown that at least six negative/positive turning points are required to calculate EC50 accurately, and it has been pointed out that anesthesiology studies using the Dixon sequential method typically have a number of 20 to 40 cases.[16] It has been reported that the EC50 of remifentanil inhibiting extubation response in female patients undergoing thyroid surgery is 1.46 ng/mL.[16] At a significance level of 0.05 and efficacy of 0.8, a minimum of 22 cases per group would be required to detect a difference of 0.2 ng/mL. Considering that there may be a 10% lost follow-up rate, we included a total of 50 patients.

Data were statistically analyzed using SPSS 26.0 software. The sequential trial data were calculated using the mean of the negative/positive inflection point method as an estimate of target concentration (EC50) in patients with 50% remifentanil suppression of extubation cough. At the same time, EC50 and its 95% Confidence Interval (CI) were calculated by Probit regression method. All indices were subjected to normality test, and those conforming to normal distribution were expressed as mean ± standard deviation. Independent sample t -test was applied for comparison between groups. The measurement data that did not conform to the normal distribution were represented by median (M) and quartile spacing (IQR), that was, M (P25~P75). Non-parametric tests were used for comparisons between groups. Count data was expressed by rate, and comparison between groups was performed by chi-square test or Fishers exact probability method. $P < 0.05$ was considered statistically significant.

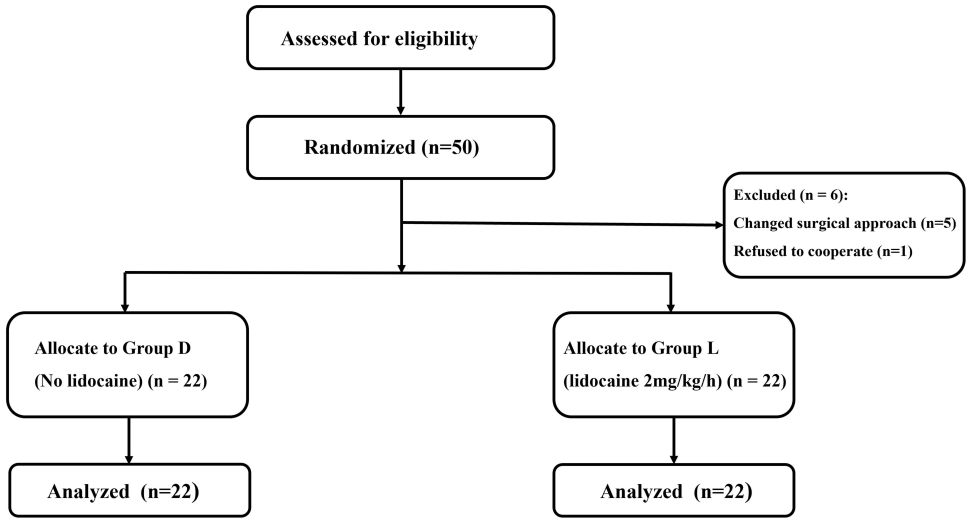

Figure 1 Flow diagram of study.

Results

The General Data of the Patients Included

Figure 1 shows the research flow diagram. Six women who changed surgical approach or refused the blood draw were withdrawn from the study. Finally, 44 patients were included in the analysis. The demographic characteristics of the patients in the two groups are presented in Table 1. The age, weight, height, ASA classification, and length of surgery in the two groups were similar ($P > 0.05$).

Determination of EC50 for Remifentanil

The sequential concentrations of remifentanil with or without lidocaine are shown in Figures 2 and 3. The EC50 values of remifentanil calculated using probit regression were 1.40 ng/mL (95% CI, 1.15–1.65 ng/mL) in Group C and 0.83 ng/mL (95% CI, 0.58–1.08 ng/mL) in Group L. The EC50 values for remifentanil calculated by the mean values of the crossover's midpoints were 1.40 ± 0.18 ng/mL in Group C and 0.83 ± 0.19 ng/mL in Group L. A significant difference was seen between the two groups ($P < 0.05$). This suggests that only a lower concentration of remifentanil can inhibit the cough reaction during intravenous lidocaine infusion.

Comparison of the Characteristics of Extubation Recovery Period Between the Two Groups

As shown in Table 2, there is no differences in the recovery time, extubation time, SpO_2 at extubation, and classification of extubation cough reaction between lidocaine group and control group ($P > 0.05$). Among the two groups, $PetCO_2$ in

Table 1 Comparison of General Data Between the Two Groups (Mean ± Standard Deviation)

Characteristic	Group C (n = 22)	Group L (n = 22)	P-value
Mean age (y)	47.09±10.98	50.09±9.58	0.340
Height (cm)	159.59±5.78	158.27±5.72	0.451
Weight (kg)	59.18±7.94	57.45±8.06	0.478
ASA classification (I/II)	8/14	12/10	0.226
The length of surgery(min)	76.18±23.91	90.14±23.94	0.060

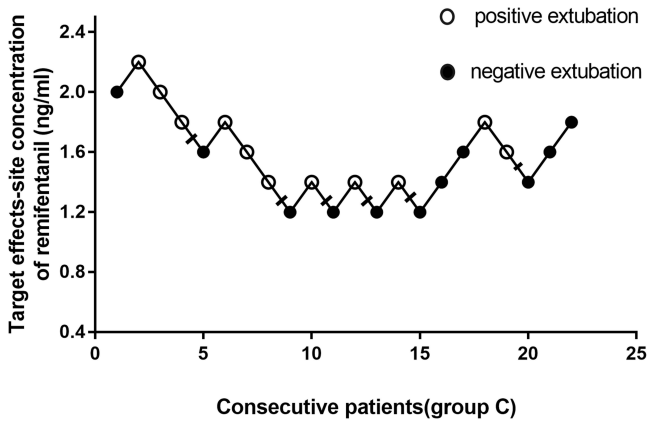

Figure 2 Stepwise dose adjustment of lidocaine for extubation cough using up-and-down method (the control group). The black dot (●) represents positive cough reaction and the white dot (○) represents negative cough reaction.

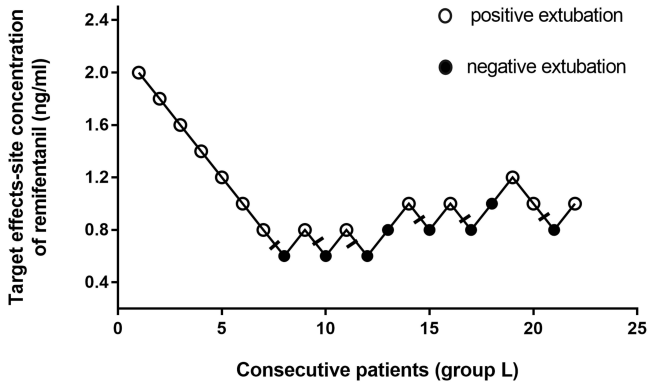

Figure 3 Stepwise dose adjustment of lidocaine for extubation cough using up-and-down method (the lidocaine group). The black dot (●) represents positive cough reaction and the white dot (○) represents negative cough reaction.

the lidocaine group was lower than that in the control group ($Z=-2.162$, $P < 0.05$). The respiratory rate of the lidocaine group after extubation was higher than that of the control group ($Z=-3.287$, $P < 0.05$). During the observation period from extubation to recovery room, oxygen saturation decreased in 5 cases in the control group, while no respiratory adverse events occurred in the lidocaine group, and the difference was statistically significant ($P < 0.05$).

Table 2 Comparison of Characteristics in Extubation Recovery Stage Between the Two Groups

	Group C (n = 22)	Group L (n = 22)	P-value
Wake up time (min)	3(2,3)	2(1.75,3)	0.146
Extubation time (min)	4(3,5)	3(3,4.25)	0.111
Classification of extubation cough reaction			0.574
0	4(18.2%)	8(36.4%)	
1	7(31.8%)	6(27.3%)	
2	9(40.9%)	7(31.8%)	
3	2(9.1%)	1(4.5%)	
$petCO_2$ at extubation (mmHg)	39.50 (36.50,42.25)	37.00 (36.75,38.00)	0.031
Respiratory rate (breaths/min).	11 (9.75,12)	12 (12,13)	0.001
SpO_2 at extubation (%)	99 (99,100)	100 (99,100)	0.051
Respiratory system after extubation adverse event	5/17	0/22	0.048

Table 3 Comparison of Pressure and Heart Rate Between Two Groups at Different Time Points

	Mean Arterial Pressure (mmHg)		P-value	Heart Rate (beats/min)		P-value
	Group C	Group L		Group C	Group L	
T_0	99.50±9.40	98.09±14.63	0.706	75.41±12.42	79.00±10.66	0.309
T_1	83.32±8.06*	84.23±11.14*	0.758	55.00±5.49*	57.50±7.088*	0.197
T_2	102.36±12.77	99.95±12.50	0.530	75.27±12.54	72.91±10.26	0.498
T_3	101.50±11.66	101.50±12.17	1.000	76.91±9.70	77.95±11.65	0.748
T_4	101.55±11.35	101.36±12.60	0.960	80.5±9.32	82.18±12.76	0.620

Notes: T0 (into the operating room), T1 (15 minutes before extubation), T2 (at tracheal extubation), T3 (1 minute after extubation), T4 (5 minutes after extubation). *$P < 0.05$ VS T_0.

Comparison of Intraoperative and Postoperative Conditions

Compared with time T0, the mean arterial pressure in Group C and Group L ($t = 7.295$, $P < 0.05$; $t = 5.848$, $P < 0.05$) and heart rate in Group C and Group L ($t = 7.976$, $P < 0.05$; $t = 7.493$, $P < 0.05$) at time T1 decreased significantly. However, there were no significant differences in mean arterial pressure and heart rate between the two groups at various time points (Table 3 and Figure 4). The drainage volume of the lidocaine group was slightly higher than that of the control group at 24h after wound operation ($T = -2.148$, $P < 0.05$). There were no significant differences in the days of drainage tube removal, hospitalization days and postoperative adverse reactions between the two groups (Supplementary Table 1). No adverse reactions associated with intravenous lidocaine, such as arrhythmia, perioral numbness, visual disturbance, and dizziness, occurred in the lidocaine group.

Discussion

Our study showed that the EC50 of remifentanil inhibiting extubation cough reaction in lidocaine group was 0.83 ng/mL (95% CI: 0.88–1.08 ng/mL), which was lower than that in control group (95% CI: 1.15–1.65 ng/mL), about 40% lower. This suggests that the combination of intravenous lidocaine reduces the concentration of remifentanil required to suppress the cough response. At the same time, the incidence of respiratory adverse after extubation in lidocaine group was lower than that in control group. This also confirms from the side that intravenous lidocaine reduces the respiratory depression, respiratory amnesia and other side effects caused by large doses of remifentanil after reducing the concentration of remifentanil. Lidocaine may inhibit coughing by inhibiting the excitation of airway C fiber receptors to reduce airway reactivity.[17] In this study, there was no difference in hemodynamics between lidocaine group and control group. This is the same as the study by Shajar,[18] which demonstrated that the concentration of remifentanil required to suppress cough is greater than the concentration required to inhibit cardiovascular response.

Lidocaine, a widely used local anesthetic, not only has characteristics such as suppressing cough, analgesia, anti-hyperalgesia, anti-inflammation, but also has the advantages of low price and high safety.[19] The incidence of coughing

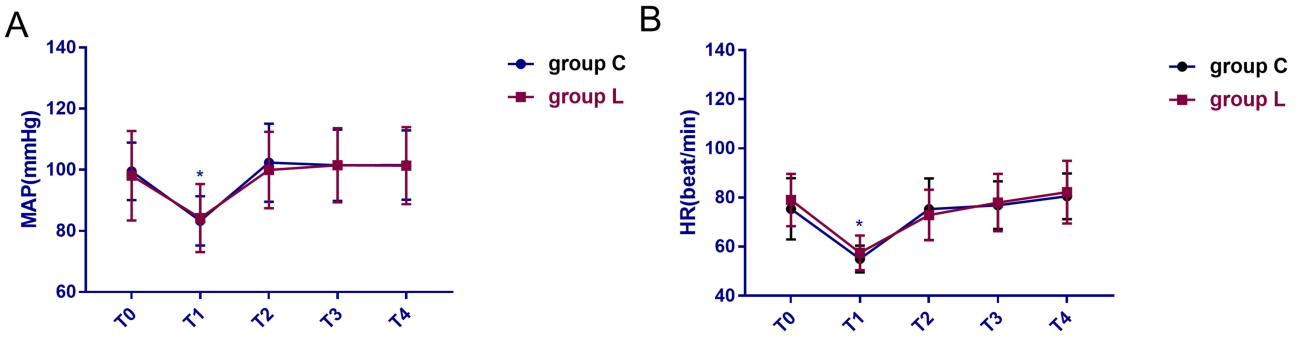

Figure 4 Trends of mean arterial pressure and heart rate at different time points in the two groups. (**A**) Mean arterial pressure at different time points in the two groups. (**B**) Heart rate at different time points in the two groups. *$P < 0.05$ vs T_0.

during emergence from general anesthesia is extremely high, and in thyroid surgery, coughing may cause serious postoperative complications such as wound dehiscence and hematoma formation. Therefore, prevention and control of coughing during tracheal extubation are of paramount importance. There are many methods to prevent and control the cough reflex during extubation, and the opioid drugs, led by remifentanil, have the best effect,[20] but they also have side effects such as respiratory depression, apnea, delayed awakening, nausea, and vomiting. This study starts from two characteristics of lidocaine intravenous infusion: on the one hand, it explores whether the combination of lidocaine can lower the EC50 of remifentanil inhibiting the cough reflex during extubation, and on the other hand, it explores whether lidocaine can alleviate postoperative pain after thyroidectomy and improve postoperative recovery.

The EC50 of remifentanil inhibiting cough response can be affected by gender, age, combined anesthetic agents and type of surgery. In this study, middle-aged and young female thyroid surgery patients were selected and sevoflurane combined with remifentanil anesthesia, excluding other interfering factors, in order to obtain more accurate remifentanil EC50. Female patients in Asia had greater incidence, prevalence, and mortality rates of thyroid cancer than male patients.[21] Compared to men, women need lower doses of remifentanil to suppress coughing.[22,23] The effect of sex on the prevention of cough by remifentanil is not related to the pharmacokinetics of remifentanil, but may be related to the difference of μ receptor between the sexes.[23]

However, there are a few limitations in the present study. First, we did not measure the precise concentration of lidocaine in plasma. Compared to other studies, we used typical doses and infusion speeds and relatively short infusion durations. Similar to previous studies, we did not observe any adverse reactions (arrhythmia, perioral numbness, visual disturbance and dizziness) associated with lidocaine, which also demonstrates that our dose is safe for clinical use. Second, we did not explore the optimal intravenous infusion dose of lidocaine. Different doses of lidocaine may have different effects on the inhibition of cough response and postoperative pain, and the optimal dose is still unknown, which needs further study.

Conclusion

Remifentanil combined with lidocaine reduced the EC50 of remifentanil by 40% for prevention of extubation cough in female patients undergoing thyroid surgery. The EC50 for cough during extubation in female patients undergoing intravenous lidocaine prophylaxis for thyroid surgery was 0.83 ng/mL.

Data Sharing Statement

The individual participant's data underlying published results reported in this study can be accessed with approval from the corresponding authors after publication.

Disclosure

The authors report no conflicts of interest in this work.

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