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Predicting effective remifentanil concentration in 95% of patients to prevent emergence cough after laryngomicroscopic surgery

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Abstract

Smooth emergence or cough prevention is a clinically important concern in patients undergoing laryngomicroscopic surgery (LMS). The purpose of this study was to estimate the effective concentration of remifentanil in 95% of patients (EC95) for the prevention of emergence cough after LMS under propofol anesthesia using the biased coin design (BCD) up-down method.

A total of 40 adult patients scheduled to undergo elective LMS were enrolled. Anesthesia induction and maintenance were performed with target-controlled infusion of propofol and remifentanil. Effective effect-site concentration (Ce) of remifentanil in 95% of patients for preventing emergence cough was estimated using a BCD method (starting from 1 ng/mL with a step size of 0.4 ng/mL). Hemodynamic and recovery profiles were observed after anesthesia.

According to the study protocol, 20 patients were allocated to receive remifentanil Ce of 3.0 ng/mL, and 20 patients were assigned to receive lower concentrations of remifentanil, from 1.0 to 2.6 ng/mL. Based on isotonic regression with a bootstrapping method, EC95 (95% CI) of remifentanil Ce for the prevention of emergence cough from LMS was found to be 2.92 ng/mL (2.72–2.97 ng/mL). Compared with patients receiving lower concentrations of remifentanil, the incidence of hypoventilation before extubation and extubation time were significantly higher in those receiving remifentanil Ce of 3.0 ng/mL. However, hypoventilation incidence after extubation and staying time in the recovery room were comparable between the 2 groups.

Using a BCD method, the EC95 of remifentanil Ce for the prevention of emergence cough was estimated to be 2.92 ng/mL (95% CI: 2.72–2.97 ng/mL) after LMS under propofol anesthesia.

Abbreviations: ASA = American Society of Anesthesiologists, BCD = biased coin design, BIS = bispectral index, Ce = effect-site concentration, LMS = laryngomicroscopic surgery, PACU = post-anesthetic care unit, PAVA = pooled-adjacent-violators algorithm, TCI = target-controlled infusion.

Keywords: cough, emergence, laryngomicroscopic surgery, remifentanil, target-controlled infusion

1. Introduction

Cough during tracheal extubation from general anesthesia may induce unexpected side effects, such as hypertension, tachycardia, or arrhythmia, increased intracranial and/or intraocular pressure, laryngospasm, wound dehiscence, and bleeding of the surgical site. In addition, laryngomicroscopic surgery (LMS) itself can directly stimulate the vocal cords, which may provoke coughing. Emergence cough can cause vocal-cord injury, which may have detrimental effects on patients, especially professional voice users. Thus, smooth emergence or cough prevention is a clinically important concern in patients undergoing LMS.

During emergence, remifentanil can be infused, because it is a potent short-acting opioid with a short context-sensitive half time and easy controllability. Previous studies have shown that low-dose remifentanil infusion could reduce cough and provide hemodynamic stability without significantly delaying emergence from propofol or isoflurane anesthesia.[1,2] Effective remifentanil effect-site concentration (Ce) in 95% of patients (EC95) for the prevention of emergence cough has been reported to range from 2.14 to 2.94 ng/mL, showing some differences according to the type of surgery, main anesthetic agent, and sex of the patient.[3–6] In LMS, the incidence of emergence cough is relatively high, and Ce of remifentanil for its suppression is also higher than for other surgeries because of direct stimuli to vocal cords by the procedure.[7] The purpose of this study was to estimate the EC95 of remifentanil Ce for prevention of emergence cough after LMS under propofol anesthesia using a biased coin design (BCD) up-down method.

2. Methods

After obtaining approval for this study by the Institutional Review Board of Ajou University Hospital (ref no.: AJIRB-MED-CT4–16-349) and registering at ClinicalTrials.gov (ref no.:

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NCT02973724), written informed consent was obtained from all patients. We included a total of 40 patients aged 19 to 65 years who were scheduled to undergo elective LMS with American Society of Anesthesiologists (ASA) physical status I or II. Exclusion criteria were: anticipated difficult airway for endotracheal intubation, severe renal, hepatic, and cardiovascular diseases, chronic obstructive lung disease, bronchial asthma, and a history of upper respiratory infection (for >2 weeks).

All patients had no premedication. Upon arrival at the operating room, routine monitors, including electrocardiography, pulse oxymetry, and noninvasive arterial blood pressure, were applied. In addition, a bispectral index sensor (BIS; Covidien LLC, Mansfield, MA) was attached to the forehead area to assess anesthetic depth. After preoxygenation with 100% O_2, remifentanil Ce of 4 ng/mL and propofol Ce of 5 μg/mL were infused using a target-controlled infusion (TCI) pump (Orchestra, Fresenius Vial, France) for anesthesia induction. Pharmacokinetic models for remifentanil and propofol TCI followed those of Minto et al[8] and Marsh et al,[9] respectively. The TCI system delivers an intravenous drug using an infusion pump controlled by a computer calculating the infusion rate according to the drug's specific pharmacokinetics, based on 3-compartment modeling. It can recalculate designated Ce frequently, and so enables us to constantly maintain and monitor the target Ce of a drug. During surgery, propofol Ce of 2.5 to 4.0 μg/mL was administered to reach the target BIS score of 40 to 60. Remifentanil Ce of 2.5 to 5.0 ng/mL was administered to maintain heart rate and systolic blood pressure within 20% of preanesthetic values.

Endotracheal intubation was performed with rocuronium of 0.6 mg/kg. The size of endotracheal tube was 6.5 mm for men and 6.0 mm for women. Cuff pressure was set between 20 and 25 cm H_2O using a pressure gauge (Hi-Lo Hand Pressure Gauge, VBM Medizintechnik, GmbH, Germany). A ventilator was set to target an end-tidal CO_2 tension ($EtCO_2$) of 35 to 40 mmHg using an air/O_2 mixture ($FiO_2 = 0.5$).

Propofol TCI was stopped at the end of surgery. Remifentanil TCI was titrated to a predetermined Ce. Throughout emergence, predetermined Ce of remifentanil was maintained at least 15 minutes until extubation. To reverse neuromuscular blockade, sugammadex of 2 mg/kg was administered after confirming reappearance of T2 response upon train of 4 stimulation. Mechanical ventilation was changed to manual ventilation with 100% O_2. $EtCO_2$ was maintained between 40 and 50 mmHg. If patients opened their eyes spontaneously or by verbal commands, and spontaneous ventilation of adequate tidal volume and respiratory rate were recovered, endotracheal extubation was performed. Immediately after extubation, remifentanil TCI was discontinued. When patient's consciousness and respiration were stably recovered, the patient was transferred to the post-anesthetic care unit (PACU).

To predict EC95 of remifentanil Ce to prevent emergence cough, a BCD method was used in this study.[10,11] Suppose the EC95 is to be calculated ($\Gamma = 0.95$); the probability $B = 1 - \Gamma/\Gamma = 1 - 0.95/0.95 = 1/19$ is defined. With this BCD method, each subsequent remifentanil Ce was based on the patient's previous response during emergence. The initial remifentanil Ce for the first patient was 1.0 ng/mL, the lowest Ce for preventing emergence cough in previous studies.[3,12] In a previous study using the up-and-down method, the standard deviation (SD) of estimated EC50 of remifentanil Ce for the prevention of emergence cough was 0.39 ng/mL.[3] Since the step size of Ce should be larger than the previous SD, it was set at 0.4 ng/mL. A sudden abdominal contraction during emergence was considered to be emergence cough. If the patient did not have an emergence cough, extubation was considered successful. Conversely, if the patient had coughs during the study period, it was defined as a failure. If a failure was observed, the predetermined Ce was stepped up for the next patient. If a success was observed, the next patient was randomized with a probability B of 1/19 of having the next lower Ce and a probability $1 - B$ of 18/19 of having the same Ce.

During emergence, 1 anesthesiologist controlled the TCI pump, and another anesthesiologist who was blinded to remifentanil Ce checked patients for coughing. Hemodynamic variables, SpO_2, and $EtCO_2$ during emergence were measured and recorded at 5 time points: before anesthesia induction (baseline, T0), at the end of surgery (T1), at eye opening (T2), immediately after extubation (T3), and 5 minutes after extubation (T4).

Hypoventilation (<8 breaths/min), laryngospasm, desaturation ($SpO_2 < 95\%$), and the time to eye opening or extubation (from time at 1.5 μg/mL of propofol Ce to eye opening or extubation) were assessed and recorded. At admission and 15 minutes after PACU, the third practitioner, who was also blinded to remifentanil Ce, assessed nausea sedation using a 4-point rating scale (1 = oriented; 2 = drowsy but responsive to commands; 3 = rouses with mild physical stimulation; 4 = sedated and unresponsive)[13] and pain score using a numerical rating scale (NRS: 0 = none and 10 = most severe imaginable). If NRS was >5 or patient requested it, fentanyl of 1 μg/kg was administered. When patient's modified Aldrete score was above 9, he or she was discharged from PACU and the staying time was recorded.

Standard calculations for choice of sample size are precluded in the BCD method by the non-independence of data and an unknown distribution. Simulation studies have shown that a group size of 20 to 40 patients provides stable estimates of the target dose for most scenarios.[14] These findings were confirmed in other BCD design studies.[15,16] Our sample size of 40 patients was based on these studies. For statistical analyses, IBM SPSS Statistics ver. 23.0 (Armonk, NY) and R code for Windows (R ver. 3.2.2) were used. Values are presented as mean ± SD for parametric continuous variables, median (interquartile range) for skewed variables, or number of patients. The normality of data distribution was analyzed using the Kolmogorov–Smirnov test. An independent t test or a Mann–Whitney U test was used to compare continuous data as appropriate. A Chi-square test or Fisher exact test was used to compare incidences of adverse events as appropriate. An isotonic regression method with a bootstrapping approach was used to estimate EC95 of remifentanil Ce and its confidence intervals (CIs).[14,17] Using a pooled-adjacent-violators algorithm (PAVA), an adjusted response probability was calculated.[10] A P value of <.05 was considered statistically significant.

3. Results

A total of 40 patients completed this study, and their data were analyzed. Patients' characteristics are summarized in Table 1. Figure 1 showed the up-and-down sequence in consecutive patients. Twenty patients were allocated to be administered 3.0 ng/mL of remifentanil Ce, and 20 patients were assigned to receive lower remifentanil concentrations from 1.0 to 2.6 ng/mL (12 patients were administered 2.6 ng/mL, 4 were administered 2.2 ng/mL, 2 were administered 1.8 ng/mL, 1 was administered 1.4 ng/mL, and 1 was administered 1.0 ng/mL). Figure 2 shows

Table 1

Characteristics of patients.

	Remi 3.0 (n = 20)	Remi ≤ 2.6 (n = 20)
Male	13	14
Age, y	46.8 [39.3–59.0]	47.3 [39.0–55.5]
Weight, kg	68.4 ± 11.5	67.7 ± 10.5
Height, cm	167.2 ± 7.1	166.4 ± 8.3
BMI, kg/m^2	24.3 ± 3.0	24.4 ± 2.5
ASA PS (I/II)	15/5	12/8

Values are expressed as mean ± SD, median [IQR], or number of patients.
ASA PS = American Society of Anesthesiologists physical status, BMI = body mass index.

PAVA response rate. From isotonic regression with a bootstrapping method, the EC95 (95% CI) of remifentanil Ce for the prevention of emergence cough from LMS was estimated to be 2.92 ng/mL (2.72–2.97 ng/mL).

Recovery profiles were described for patients receiving remifentanil at <3.0 ng/mL (1.0, 1.4, 1.8, 2.2, and 2.6 ng/mL) versus those who received remifentanil at 3.0 ng/mL, the closest value to the estimated ED95 in this study. Compared with patients receiving remifentanil Ce at ≤2.6 ng/mL, the incidences of hypoventilation before extubation and pain score in the PACU were significantly higher, and extubation time was significantly longer in those receiving remifentanil Ce of 3.0 ng/mL. However, hypoventilation incidents after extubation and staying time in PACU were comparable between the 2 groups (Table 2).

Table 3 shows hemodynamic variables, respiratory rate, and $EtCO_2$ during emergence. Compared with patients receiving remifentanil Ce of ≤2.6 ng/mL, respiratory rates were significantly lower at T2 (eye opening) and T3 (immediately after extubation), whereas $EtCO_2$ was significantly higher at T2 in those receiving remifentanil Ce of 3.0 ng/mL. However, all variables at T4 (5 minutes after extubation) were comparable between the 2 groups.

4. Discussion

In this study, the EC95 of remifentanil Ce for the prevention of emergence cough was found to be 2.92 ng/mL (95% CI; 2.72–2.97 ng/mL) after LMS under propofol anesthesia. Half of the patients received remifentanil Ce of 3.0 ng/mL in this study. This concentration was very close to the estimated EC95 for cough prevention after LMS. Although patients receiving remifentanil of 3.0 ng/mL had longer extubation time with more hypoventilation before extubation, these patients comparably recovered their respiratory rates after extubation without delaying discharge from PACU compared with the other patients who received a lower dose of remifentanil (≤2.6 ng/mL).

Cough reflex results from stimulation of stretch receptors under tracheal epithelium via the vagus nerve and central nervous system. Emergence cough from general anesthesia after LMS might be associated with serious complications, such as wound dehiscence and bleeding.[18] Remifentanil has a centrally mediated antitussive effect by inhibiting brain-stem opioid receptors.[19] It has been reported that remifentanil can allow stable recovery from general anesthesia without causing hemodynamic instability or cough in previous studies.[3–6] Moreover, remifentanil TCI works better than lidocaine, a popular antitussive agent, during anesthesia emergence.[20] Remifentanil administration using TCI may provide more predictable and reliable cough prevention because it can reach a defined target Ce with acceptable levels of bias and inaccuracy.[21]

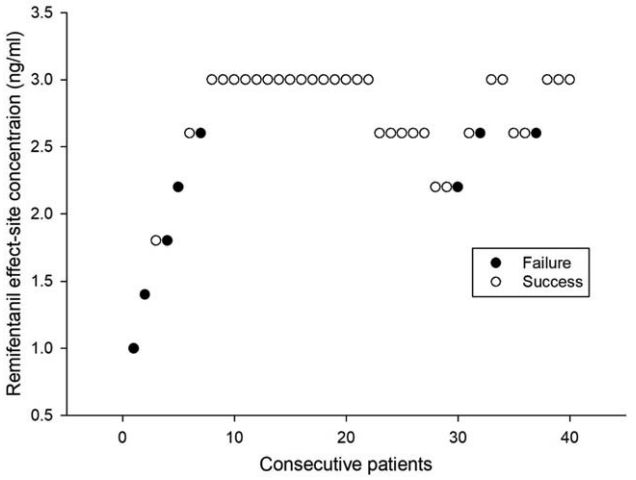

Figure 1. Consecutive remifentanil effect-site concentrations using a biased coin design.

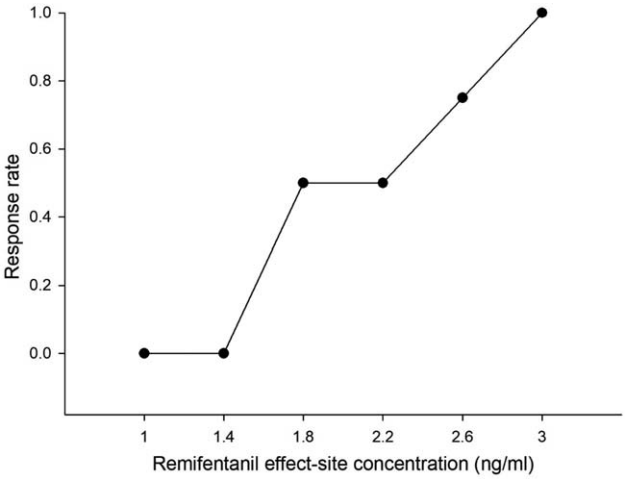

Figure 2. Pooled-adjacent-violators algorithm response rate.

Table 2

Recovery profiles.

	Remi 3.0 (n = 20)	Remi ≤ 2.6 (n = 20)	*P* value
No cough/cough	20/0	12/8	.002
Operation time, min	20.8 ± 10.7	16.0 ± 12.7	.209
Anesthesia time, min	55.8 ± 12.0	48.8 ± 15.4	.116
Eye opening time, min	5.9 ± 1.6	5.0 ± 1.3	.084
Extubation time, min	7.9 ± 1.9	6.2 ± 1.5	.005
Hypoventilation			
Before extubation	14 (70%)	7 (35%)	.027
After extubation	4 (20%)	1 (5%)	.151
PACU			
Staying time, min	36.0 ± 4.8	35.5 ± 3.9	.719
Pain score	3 [1.25–4]	2 [1–3]	.033

Values are expressed as mean ± SD, median [IQR], or number of patients (%).
Remi 3.0 = patients received remifentanil Ce of 3.0 ng/mL, Remi ≤2.6 = patients received remifentanil Ce of 1.0 to 2.6 ng/mL, PACU = post-anesthetic care unit, pain score assessed by an 11-point numerical rating scale (0 = none and 10 = most severe imaginable) at 15 minutes after PACU arrival.

Table 3

Hemodynamic data, respiratory rate, and end-tidal CO_2 tension during emergence.

		T0	T1	T2	T3	T4
MAP, mmHg	Remi 3.0	101.6 ± 12.4	86.1 ± 13.7	78.6 ± 10.3	89.5 ± 13.1	88.0 ± 12.8
	Remi ≤2.6	107.0 ± 12.4	93.1 ± 9.3	85.3 ± 12.4	97.4 ± 13.4	91.8 ± 12.8
HR, beats/min	Remi 3.0	74.6 ± 13.8	66.3 ± 10.8	63.6 ± 13.2	70.9 ± 10.9	65.2 ± 10.8
	Remi ≤2.6	73.7 ± 14.1	74.1 ± 10.2	69.7 ± 14.0	76.8 ± 14.3	69.6 ± 10.0
RR, breaths/min	Remi 3.0		9.6 ± 1.5	6.7 ± 2.2*	8.9 ± 1.4*	10.4 ± 2.0
	Remi ≤2.6		10.0 ± 1.4	9.8 ± 3.7	11.0 ± 2.3	11.4 ± 1.8
$EtCO_2$, mmHg	Remi 3.0		36.1 ± 1.4	45.2 ± 4.6*	42.9 ± 4.2	41.6 ± 4.6
	Remi ≤2.6		36.1 ± 2.8	41.7 ± 4.8	41.1 ± 5.7	40.2 ± 4.4

Values are expressed as means ± SD.

MAP = mean arterial pressure, HR = heart rate, RR = respiratory rate, $EtCO_2$ = end-tidal CO_2 tension, T0 = baseline, T1 = at the end of surgery, T2 = at the eye opening, T3 = immediately after extubation, T4 = 5 minutes after extubation.

* $P < .05$ versus remi ≤2.6 ng/mL.

An earlier study by Chang et al[7] has shown that remifentanil TCI can decrease the incidence of cough from 91% at 1.0 ng/mL of remifentanil Ce to 57% and 46% at 1.5 and 2.0 ng/mL, respectively. There was no severe cough after remifentanil administration at 2.0 ng/mL. Although they demonstrated that remifentanil TCI could dose-dependently decrease the severity and incidence of emergence cough after LMS, they only reported that remifentanil Ce of 2.0 ng/mL approximated effective concentration in 50% of patients (EC50).[7] They did not suggest that EC95 should be more important for physicians than EC50. This study demonstrated that the EC95 of remifentanil to prevent emergence cough from propofol anesthesia after LMS was 2.92 ng/mL. This dose is considerably higher than those of previous studies.[3,5] A report on thyroid surgery using Dixon up-and-down method showed that EC95 of remifentanil was 2.14 ng/mL.[3] Another study on trans-sphenoidal hypophysectomy using a BCD method reported that EC95 of remifentanil was 2.51 ng/mL from propofol anesthesia.[5] These differences might result from the direct stimulation of the vocal cord by LMS itself in the present study.

EC95 of remifentanil Ce for suppressing emergence cough may depend on the type of anesthetics, the sex of the patient, the study design, such as Dixon method and BCD design, and various clinical conditions. Remifentanil EC95 to prevent emergence cough from propofol anesthesia was significantly lower than that from desflurane anesthesia,[6] perhaps because of an intrinsic cough suppression effect of propofol.[22] Meanwhile, men had a significantly higher EC50 of remifentanil Ce for suppressing emergence cough than women,[23] perhaps because of sex differences in opioid requirements for similar clinical situations.[24] The study design might have influenced the prediction for remifentanil EC95. Previous studies have used EC95 of remifentanil to prevent cough from general anesthesia using Dixon up-and-down method.[3,4] Basically, the Dixon up-and-down method is a simplified strategy to estimate the median effective dose, volume, or concentration. By targeting the 50th quantile, it is difficult to accurately estimate the quantiles far from the midpoint. As a back-up analysis, probit or logistic regression is often applied, but this strategy leads to significant bias in the estimation of high quantiles.[10] Because a BCD method can better estimate the concentration directly at any quantiles than Dixon method can, it should be considered first for estimating high quantiles, such as EC95.[10,11,14] Therefore, the BCD method was adopted to predict EC95 in this study. In addition, half of the enrolled patients in this study received remifentanil at 3.0 ng/mL, which was very close to the remifentanil EC95 value (2.92 ng/mL) to prevent cough. Thus, recovery profiles and other side effects, such as hypoventilation and hypercapnia, during remifentanil TCI at EC95 could be observed in this study. This is another advantage of the BCD method. Since remifentanil infusion during emergence might potentiate sedative and hypnotic effects of propofol,[25] delayed emergence might occur. Compared with those receiving 2.6 ng/mL or less of remifentanil Ce, patients receiving 3.0 ng/mL of remifentanil Ce had a significantly higher incidence of hypoventilation before extubation (70% vs 35%) with significantly longer extubation time (7.9 ± 1.9 vs 6.2 ± 1.5 minutes), although there was no significant difference in the incidence of hypoventilation after extubation or PACU staying time between the 2 groups. Therefore, remifentanil TCI at a relatively high concentration of 3.0 ng/mL for smooth emergence or prevention of cough requires special attention to possible respiratory depression and delayed extubation.

This study has a few limitations. First, we used the calculated Ce of remifentanil by a pharmacokinetic model regardless of pharmacodynamics variability instead of using a measured vale of Ce. Second, the postoperative pain score was significantly higher in patients receiving remifentanil at 3.0 ng/mL than in those receiving lower doses of remifentanil in this study. Some studies have reported that high-dose remifentanil infusion is associated with opioid-induced hyperalgesia.[26,27] Further studies are needed to elucidate the association between postoperative pain and high-dose remifentanil infusion during emergence.

In conclusion, the EC95 of remifentanil TCI to prevent cough during emergence was found to be 2.92 ng/mL after LMS under propofol anesthesia. Since remifentanil infusion at this concentration might delay extubation time and increase the risk of hypoventilation, special attention is needed.

Author contributions

Conceptualization: Hyun Jeong Kwak.
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