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 hypventilation before extubation and extubation time were significantly higher in those receiving remifentanil Ce of 3.0 ng/mL. However, hypventilation 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.:
drug. During surgery, propofol \( Ce \) of 2.5 to 4.0 enables us to constantly maintain and monitor the target \( Ce \) of a modeling. It can recalculate designated \( Ce \) frequently, and so delivers an intravenous drug using an infusion pump controlled by a computer calculating the infusion rate according to the unknown distribution. Simulation studies have shown that a computer calculating the infusion rate according to the drug’s specific pharmacokinetics, based on 3-compartment modeling. It can calculate 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 \( \mu \)g/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 (Et\( CO_2 \)) of 35 to 40 mmHg using an air/O\( _2 \) mixture (Fi\( O_2 \)=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% \( O_2 \). Et\( CO_2 \) 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 EC\( 95 \) of remifentanil \( Ce \) to prevent emergence cough, a BCD method was used in this study.\(^{1,10,11} \) Suppose the EC\( 95 \) is to be calculated (I\( r=0.95 \); the probability \( B = 1 - I^{1/2} = 1 - 0.95/0.95 = 1/19 \) 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.\(^{1,10} \) In a previous study using the up-and-down method, the standard deviation (SD) of estimated EC\( 50 \) of remifentanil \( Ce \) for the prevention of emergence cough was 0.39 ng/mL.\(^{13} \) 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 Et\( CO_2 \) during emergence were measured and recorded at 5 time points: before anesthesia induction (baseline, \( T_0 \)), at the end of surgery (\( T_1 \)), at eye opening (\( T_2 \)), immediately after extubation (\( T_3 \)), and 5 minutes after extubation (\( T_4 \)).

Hypoventilation (<8 breaths/min), laryngospasm, desaturation (\( SpO_2 < 95 \% \)), and the time to eye opening or extubation (from time at 1.5 \( \mu \)g/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 scale; 1=oriented; 2=drowsy but responsive to command; 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 \( \mu \)g/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 EC\( 95 \) 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/m²               | 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 hypventilation 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 3 shows hemodynamic variables, respiratory rate, and EtCO₂ 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 EtCO₂ 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.[15–6] 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]

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           | .0005   |
| 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.
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 propofol anesthesia. Since remifentanil infusion during emergence might potentiate sedative and hypnotic effects of propofol,\(^{21,23}\) 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 hypventilation 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 hypventilation 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 value 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 Ce for suppressing emergence cough 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 hypventilation, special attention is needed.

### Author contributions
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### References
1. Nho JS, Lee SY, Kang JM, et al. Effects of maintaining a remifentanil infusion on the recovery profiles during emergence from anesthesia and tracheal extubation. Br J Anaesth 2009;103:817–21.
2. Aouad MT, Al-Alami AA, Nasr VG, et al. The effect of low-dose remifentanil on responses to the endotracheal tube during emergence from general anesthesia. Anesth Analg 2009;108:1157–60.
[3] Lee B, Lee JR, Na S. Targeting smooth emergence: the effect site concentration of remifentanil for preventing cough during emergence during propofol-remifentanil anaesthesia for thyroid surgery. Br J Anaesth 2009;102:775–8.

[4] Lee SY, Yoo JY, Kim JY, et al. Optimal effect-site concentration of remifentanil for preventing cough during removal of the double-lumen endotracheal tube from sevoflurane-remifentanil anaesthesia: a prospective clinical trial. Medicine (Baltimore) 2016;95:e3878.

[5] Choi SH, Min KT, Lee JR, et al. Determination of EC95 of remifentanil for smooth emergence from propofol anesthesia in patients undergoing transphenoidal surgery. J Neurosurg Anesthesiol 2015;27:160–6.

[6] Lee JH, Choi SH, Choi YS, et al. Does the type of anesthetic agent affect remifentanil effect-site concentration for preventing endotracheal tube-induced cough during anesthetic emergence? Comparison of propofol, sevoflurane, and desflurane. J Clin Anesth 2014;26:466–74.

[7] Chang CH, Lee JW, Choi JR, et al. Effect-site concentration of remifentanil to prevent cough after laryngomicrosurgery. Laryngoscope 2013;123:3105–9.

[8] Minto CF, Schneider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 1997;86:10–23.

[9] Marsh B, White M, Morton N, et al. Pharmacokinetic model driven infusion of propofol in children. Br J Anaesth 1991;67:41–8.

[10] Pace NL, Stylianou MP. Advances in and limitations of up-and down methodology: a prospective clinical use, study design, and dose estimation in anesthesia research. Anesthesiology 2007;107:144–52.

[11] Durham SD, Flournoy N, Rosenberger WF. A random walk rule for phase I clinical trials. Biometrics 1997;53:745–60.

[12] Jun NH, Lee JW, Song JW, et al. Optimal effect-site concentration of remifentanil for preventing cough during emergence from sevoflurane-remifentanil anaesthesia. Anaesthesia 2010;65:930–5.

[13] Ne‘methy M, Paroli L, Williams-Russo PG, et al. Assessing sedation with regional anesthesia: inter-rater agreement on a modified Wilson sedation scale. Anesth Analg 2002;94:723–8.

[14] Stylianou M, Flournoy N. Dose finding using the biased coin up-and-down design and isotonic regression. Biometrics 2002;58:171–7.

[15] Olutoye OA, Yu X, Govindan K, et al. The effect of obesity on the ED (95) of propofol for loss of consciousness in children and adolescents. Anesth Analg 2012;115:147–53.

[16] George RB, McKeen D, Columb MO, et al. Up-down determination of the 90% effective dose of phenylephrine for the treatment of spinal anesthesia-induced hypotension in parturients undergoing cesarean delivery. Anesth Analg 2010;110:154–8.

[17] Dillen M, Heimann G, Hirsch I. Non-parametric estimators of a monotonic dose-response curve and bootstrap confidence intervals. Stat Med 2003;22:869–82.

[18] Golub JS, Hapner E, Johns MM3rd. Vocal fold hemorrhage observed during laryngoscopy. Ear Nose Throat J 2006;85:148.

[19] Mazzone SB, Undem BJ. Cough sensors. V. Pharmacological modulation of cough sensors. Handb Exp Pharmacol 2009;187:99–127.

[20] Lee JH, Koo BN, Jeong JJ, et al. Differential effects of lidocaine and remifentanil on response to the tracheal tube during emergence from general anesthesia. Br J Anaesth 2011;106:410–5.

[21] Mertens MJ, Engbers FH, Burm AG, et al. Predictive performance of computer-controlled infusion of remifentanil during propofol/remifentanil anaesthesia. Br J Anaesth 2003;90:332–41.

[22] Hans P, Marechal H, Bonhomme V. Effect of propofol and sevoflurane on coughing in smokers and non-smokers awakening from general anaesthesia at the end of a cervical spine surgery. Br J Anaesth 2008;101:731–7.

[23] Soh S, Park WK, Kang SW, et al. Sex differences in remifentanil requirements for preventing cough during anesthetic emergence. Yonsei Med J 2014;55:807–14.

[24] Dahan A, Kest B, Waxman AB, et al. Sex-specific responses to opiates: animal and human studies. Anesth Analg 2008;107:83–95.

[25] Kern SE, Xie G, White JL, et al. A response surface analysis of propofol-remifentanil pharmacodynamic interaction in volunteers. Anesthesiology 2004;100:1373–81.

[26] Flitzer D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. Br J Anaesth 2014;112:991–1004.

[27] Song YK, Lee C, Seo DH, et al. Interaction between postoperative shivering and hyperalgesia caused by high-dose remifentanil. Korean J Anesthesiol 2014;66:44–51.