

Effect-site concentration of remifentanyl for preventing cough during emergence in elderly patients undergoing nasal surgery: a comparison with adult patients

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Purpose: Prevention of cough during emergence after nasal surgery is important for avoiding surgical site bleeding. We investigated the remifentanyl effect-site concentration in 50% (EC50) of the elderly patients undergoing nasal surgery for smooth emergence without cough and compared it with that of adult patients.

Methods: Twenty-two elderly (aged 65–80 years) and 25 adult patients (aged 20–60 years) with an American Society of Anesthesiologists physical status I/II undergoing nasal surgery were enrolled. Anesthesia was maintained with sevoflurane and remifentanyl. Remifentanyl EC50 and EC95 for preventing cough were determined using the modified Dixon's up-and-down method and isotonic regression with bootstrapping approach. Recovery profiles were also recorded.

Results: With Dixon's up-and-down method, the EC50 of remifentanyl in elderly patients (2.40±0.25 ng/mL) was not significantly different from that of adults (2.33±0.30 ng/mL) ($P=0.687$). With isotonic regression, the EC95 of remifentanyl in elderly patients (3.32 [95% confidence interval: 3.06–3.38] ng/mL) was not significantly different from that of adults (3.30 [95% confidence interval: 2.96–3.37] ng/mL). However, eye opening time (14.1±3.8 vs 12.0±2.9 seconds), extubation time (17.2±4.1 vs 14.0±3.0 seconds), and postanesthesia care unit duration (44.5±7.6 vs 38.7±3.4 minutes) in elderly patients were significantly longer than those in adults ($P<0.05$).

Conclusion: Remifentanyl EC50 for preventing cough after nasal surgery with sevoflurane anesthesia did not differ between elderly and adult patients. However, delayed awakening and respiratory adverse events may warrant attention in elderly patients.

Keywords: sevoflurane, cough, remifentanyl, elderly, extubation

Introduction

Cough suppression during emergence and tracheal extubation after general anesthesia has become an important issue in patient safety. Cough due to mechanical irritation of the endotracheal tube and cuff can be accompanied by various adverse effects such as laryngospasm, hypertension, tachycardia, arrhythmia, and an increase in intracranial, intraocular, or intra-abdominal pressure.¹ Consequently, this can lead to myocardial ischemia, disruption of wound, and bleeding at the surgical site. Alongside medical development, an increasing number of elderly patients undergo surgery and exhibit a greater prevalence of cardiovascular disease than younger patients.^{2,3} Therefore, the application of agents for cough suppression during emergence should be investigated further.

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Remifentanyl is a selective μ -receptor opioid agonist with a very rapid onset time. Its extrahepatic metabolism by non-specific esterase results in rapid clearance.^{4,5} Maintenance of remifentanyl infusion during emergence has been reported to be an effective method for reducing cough and cardiovascular change without delay of recovery.^{6,7} In previous studies, the effective effect-site concentration for 95% of adults (EC95) for preventing cough has been shown to vary according to anesthetic agent, type of surgery, and patient sex, and is ranging from 2.14 to 2.94 ng/mL.^{8–10}

The aging process may alter not only the pharmacokinetics and pharmacodynamics,^{11,12} resulting in potentially variable responses to anesthetic drugs (likely increase in sensitivity), but also cough reflex.¹³ The hypothesis of this study is that altered pharmacokinetics and cough sensitivity in elderly patients may require the titration of remifentanyl target controlled infusion (TCI) for cough suppression during emergence. To the best of our knowledge, no studies to date have confirmed the effect of remifentanyl TCI on cough suppression in the elderly. Therefore, the purpose of this study is to determine the effect-site concentration of remifentanyl in 50% (EC50) of elderly patients undergoing nasal surgery for cough suppression during emergence after balanced anesthesia with sevoflurane and remifentanyl. In addition, we have compared the difference in effect-site concentration of remifentanyl and recovery profiles between elderly and adult patients.

Patients and methods

Patients

Approval was obtained from the Institutional Review Board of Ajou University Hospital (Suwon, Korea), and the study was registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT No: 02334046). All patients provided informed written consent. Twenty-two elderly patients (aged 65–80 years) and 25 adult patients (aged 20–60 years) with an American Society of Anesthesiologists physical status I or II undergoing nasal surgery (endoscopic sinus surgery or septoplasty) were enrolled in this study. The following patients were excluded from the study: those with predicted difficult airway, body mass index >30 kg/m², history of obstructive sleep apnea, chronic respiratory disease or coughing, current smokers, and angiotensin-converting enzyme inhibitor users.

Anesthesia

Patients were not administered with any premedication. Upon arrival in the operating theater, all patients were monitored via electrocardiography, pulse oximetry, automated noninvasive blood pressure measurement, and bispectral index (BIS)

using the BIS™ Quatro Sensor (Covidien, Boulder, CO, USA) applied to the forehead of each patient. After preoxygenation with 100% oxygen for 1 minute, anesthesia was induced with a bolus injection of 1.5–2.0 mg/kg propofol and 2.0–3.0 ng/mL effect-site concentration of remifentanyl via a TCI system (Orchestra®, Fresenius Vial, France) using Minto's model.¹⁴ After loss of consciousness, 0.6 mg/kg rocuronium was injected and then intubation was performed with a cuffed endotracheal tube (internal diameter 7.5 mm for males and 7.0 mm for females). The intracuff pressure was adjusted to 20–25 mmHg using a pressure gauge (Hi-Lo Hand Pressure Gauge, VBM Medizintechnik, GmbH, Germany). Anesthesia was maintained with 1.5–2.5 vol% sevoflurane and 2.0–4.0 ng/mL of remifentanyl to target a BIS between 40 and 60, and a mean blood pressure and heart rate within 20% of baseline values. Mechanical ventilation was adjusted to maintain an end-tidal CO₂ between 35 and 40 mmHg using 0.5 fraction of inspired oxygen. Corticosteroids which could affect the results were not administered during surgery. Approximately 15 minutes before the end of surgery, sevoflurane was adjusted to 1–1.2 vol% to achieve a BIS of ~60, and remifentanyl was set at the predetermined effect-site concentration for obtaining equilibrium between plasma and effect-site at the time of surgery completion. After surgery, sevoflurane was discontinued and 0.004 mg/kg glycopyrrolate and 0.02 mg/kg neostigmine were injected for reversal of residual muscle relaxation after achieving a train-of-four ratio of 0.9. Oropharyngeal suction was gently performed before injection of reversal agents. Mechanical ventilation was switched to manual ventilation to maintain an end-tidal CO₂ between 40 and 45 mmHg. Extubation was performed when patients were able to open their eyes on command and following the recovery of adequate spontaneous ventilation. Immediately after extubation, remifentanyl infusion was stopped and 100% oxygen was administered via a face mask for 5 minutes. The presence of cough was recorded by the investigator who was unaware of the concentration of remifentanyl. After confirmation of consciousness and adequate respiration, patients were transferred to the post-anesthetic care unit (PACU). In the PACU, fentanyl 1 μ g/kg was administered when the pain score exceeded 5 points on the numerical rating scale. Patients were discharged from the PACU when Aldrete score was ≥ 9 .¹⁵

Determination of effect-site concentration and recovery profiles

The Dixon's up-and-down method was used to determine the effect-site concentration of remifentanyl for cough suppression during the emergence period (in the presence of

endotracheal tube, during tracheal extubation, and 5 minutes after extubation).¹⁶ If coughing occurred during the emergence period, it was considered a failure of cough suppression. The initial effect-site concentration of remifentanyl was 1.8 ng/mL. In the next patient, the effect-site concentration of remifentanyl was determined by the success or failure of cough suppression of the previous patient. If cough suppression was a success, then the effect-site concentration of remifentanyl was reduced by 0.4 ng/mL, while in case of failure it was increased by 0.4 ng/mL. The remifentanyl EC₅₀ of patients, which enabled successful cough suppression, was determined by calculating the mean of the midpoint effect-site concentration of all independent pairs after six crossover points were obtained (ie, success to failure).

Hemodynamic data and respiratory profiles were recorded before anesthesia induction (baseline), at the end of surgery, at eye opening, immediately after extubation, and 5 minutes after extubation. The eye opening and extubation times were also measured and events of hypoventilation <8 breaths/min or oxygen saturation (SaO₂) below 95% were recorded.

Statistical analysis

The sample size was decided based on prior literature about the modified Dixon's up-and-down method. To minimize the inaccuracy of the individual study, more than the minimum six crossover points are required in this method.¹⁷

Statistical analyses were performed using the Statistical Package for Social Sciences (version 20.0 for Windows; IBM Corporation, Armonk, NY, USA) and R for Windows (version 3.0.1; The R Foundation for Statistical Computing; <https://www.r-project.org>). The EC₅₀ calculated from the modified Dixon's up-and-down method was compared between the two patient groups using a *t*-test. For backup analysis, the data were analyzed using the isotonic regression method to estimate EC₅₀ and EC₉₅ along with 95% confidence intervals (CIs). The isotonic regression is a variant of restricted least squares regression to constrain the point estimates to either increase or decrease monotonically, which has favorable statistical properties.¹⁸ The CI was estimated using the bootstrapping approach.¹⁸ All other variables were compared between groups using an independent *t*-test, chi-square test, Fisher's exact test, or Mann-Whitney *U* statistic, where appropriate. Hemodynamic data were analyzed with repeated measures of analysis of variance. Data were presented as the mean ± standard deviation or the number of patients. Statistical significance was accepted when the *P*-value was <0.05.

Results

In total, 47 patients completed the study (Figure 1). The elderly patient group comprised 22 patients with a mean age of 69 (range: 65–80 years) and the adult patient group comprised 25 patients with a mean age of 35 (range: 20–60 years).

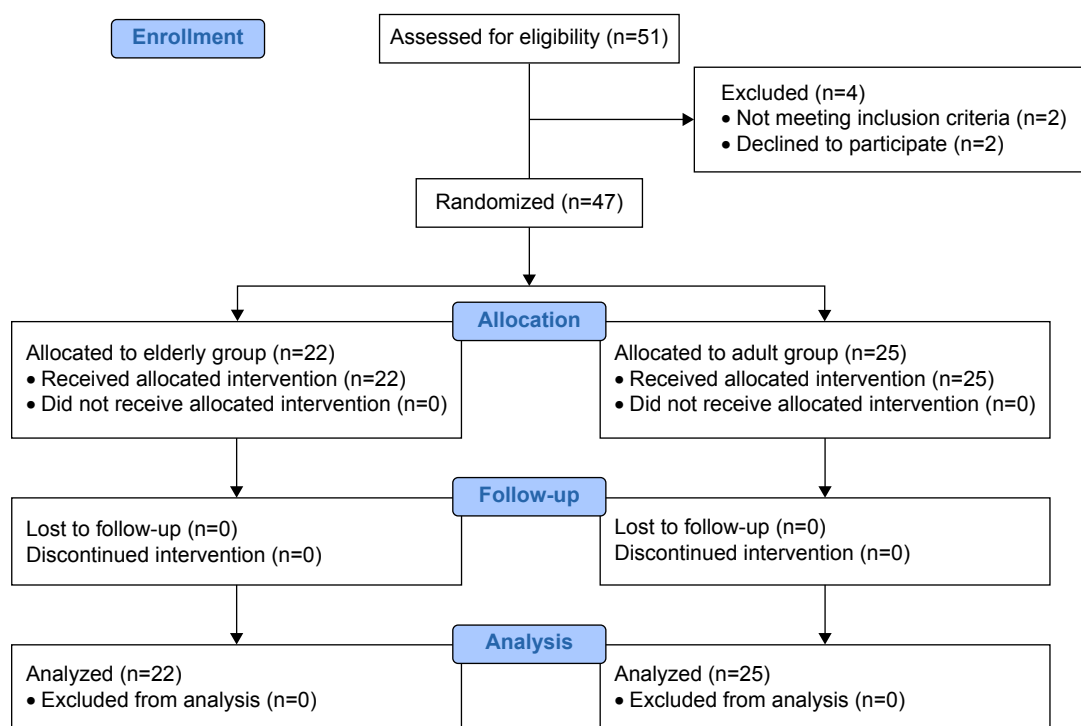


Figure 1 Consort flow diagram.

Table 1 Patient characteristics

Variables	Elderly patients (n=22)		Adult patients (n=25)	
	Success	Failure	Success	Failure
Sex (males/females)	5/5	10/2	9/3	10/3
Age (years)	67.9±2.8	70.5±4.2	37.4±12.9	32.8±11.0
Weight (kg)	66.0±10.0	64.4±10.3	67.8±13.5	72.1±11.2
Height (cm)	160.4±9.8	165.8±8.2	170.7±7.5	171.6±8.4
ASA physical status (I/II/III)	2/8	3/9	11/1	11/2

Notes: Values are expressed as mean ± standard deviation or number. ASA I is defined as a normal healthy patient; ASA II is defined as a patient with mild systemic disease.

Abbreviation: ASA, American Society of Anesthesiologists.

Patient characteristics are presented in Table 1. There were significantly more patients in the elderly groups with an American Society of Anesthesiologists physical status of II than in the adult group ($P<0.001$). During mask ventilation and intubation, there was no unpredicted difficult airway.

The sequence of dose–response data for each patient is shown in Figure 2. Using the modified Dixon's up-and-down method, the EC₅₀ of remifentanyl was not significantly different between the elderly and adult groups (2.40 ± 0.25 vs 2.33 ± 0.30 ng/mL, respectively, $P=0.687$). With isotonic regression and the bootstrapping approach, the EC₅₀ of remifentanyl was similar between the elderly and adult groups (2.50 [95% CI: 2.38 – 2.75] ng/mL and 2.52 [95% CI: 2.29 – 2.78] ng/mL, respectively). The EC₉₅ of remifentanyl was also similar between the elderly and adult groups (3.32 [95% CI: 3.06 – 3.38] ng/mL and 3.30 [95% CI: 2.96 – 3.37] ng/mL, respectively).

Recovery profiles are presented in Table 2. While the number of patients presenting cough and the effect-site concentration of remifentanyl for cough suppression

were similar between patient groups, eye opening time (14.1 ± 3.8 vs 12.0 ± 2.9 seconds), extubation time (17.2 ± 4.1 vs 14.0 ± 3.0 seconds), and PACU duration (44.5 ± 7.6 vs 38.7 ± 3.4 minutes) in the elderly group were significantly longer than those in the adult group (all $P<0.05$). There were no significant differences in pain score and additional analgesic requirement in the PACU between groups.

There were no significant differences in hemodynamic data between elderly and adult patient groups (data not shown). In the present study, the highest concentration of remifentanyl used was 3.4 ng/mL and the lowest concentration was 1.8 ng/mL. Hypoventilation (<8 breaths/min, respiratory rate) occurred in 8/22 (36%) patients in the elderly group and 6/25 (24%) patients in the adult group. Oxygen desaturation ($\text{SaO}_2 < 95\%$) occurred in one patient in the elderly group, but did not occur in the adult patient group. While these adverse events occurred more frequently in the elderly group, there were no significant intergroup differences.

Discussion

Our results showed that maintaining remifentanyl during emergence was an effective method for smooth emergence and the required effect-site concentration of remifentanyl in elderly patients was not different from that of the adult patients.

Previous studies have investigated the EC₅₀ and EC₉₅ of remifentanyl TCI for cough prevention in various surgeries.^{8,9} Choi et al⁸ reported the EC₅₀ and EC₉₅ of remifentanyl at 2.17 and 2.94 ng/mL, respectively, in males aged 18–60 years (median age 35 years) undergoing nasal surgery after balanced anesthesia with sevoflurane. These results are comparable to the present findings. Our study demonstrated that the EC₅₀ of remifentanyl in adult and

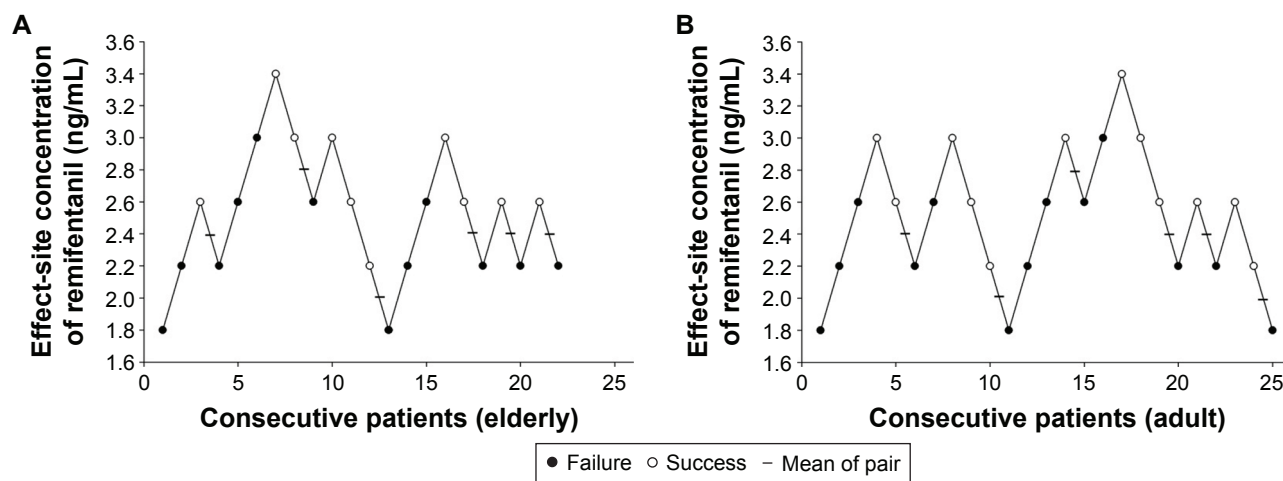


Figure 2 Sequences of effect-site concentration of remifentanyl for preventing cough during emergence.

Notes: Horizontal bars represent crossover midpoints (ie, success to failure). The effective effect-site concentration for 50% of patients (EC₅₀) of remifentanyl in the (A) elderly and (B) adult patient groups was 2.40 ± 0.25 and 2.33 ± 0.30 ng/mL, respectively.

Table 2 Recovery profiles

Variables	Elderly patients (n=22)	Adult patients (n=25)	P-value
Operation time (min)	34.1±11.5	35.2±14.8	0.777
Anesthesia time (min)	70.4±12.1	71.9±17.1	0.733
Eye opening (min)	14.1±3.8	12.0±2.9	0.035
Extubation time (min)	17.2±4.1	14.0±3.0	0.004
PACU stay (min)	44.5±7.6	38.7±3.4	0.002
Pain at PACU (NRS)	3 (3–4)	3 (3–4.25)	0.302
Additional analgesics	4	4	0.835
SaO ₂ <95%	1	0	0.468
RR <8 breaths/min	8 (36%)	6 (24%)	0.355

Note: Values are expressed as mean ± standard deviation, median (interquartile range), or number of patients (%).

Abbreviations: NRS, numerical rating scale; PACU, postanesthetic care unit; RR, respiratory rate; SaO₂, oxygen saturation; min, minutes.

elderly patients was 2.33 and 2.40 ng/mL, respectively, without significant intergroup differences. In another study,⁹ the EC95 of remifentanyl TCI was 2.51 ng/mL in patients (aged 20–65 years; mean: 43 years) undergoing transsphenoidal surgery during propofol and remifentanyl anesthesia, using biased coin up-and-down sequential allocation and the isotonic regression method.

The effect of aging on cough reflex remains controversial.^{13,19,20} A previous study demonstrated that the sensitivity of cough reflex significantly decreased in the elderly patients compared with that in the young patients,¹³ whereas other studies failed to detect this association.^{19,20} The aging process may also alter pharmacokinetics and pharmacodynamics,^{11,12} and can affect clinical responses to drugs. In general, the elderly are expected to be more sensitive to many drugs, especially opioids. Sensitivity to remifentanyl has been reported to be high in elderly patients.^{14,21} The TCI of remifentanyl is age variable-adjusted because Minto's model was based on the electroencephalogram (EEG) effect of remifentanyl using a three-compartment model with height, weight, and age as covariates.¹⁴

The present study demonstrated that there was no age-related difference in the effect-site concentration of remifentanyl for cough suppression during emergence. This suggests that remifentanyl TCI using Minto's model is appropriate to predict the clinical performance on cough suppression; therefore, there is no need to reduce the effect-site concentration of remifentanyl in the elderly. The antitussive effect of narcotics appears to be via opioid receptors such as μ - and κ -receptors^{22,23} and, at the subtype level, the antitussive effect of μ -receptors is depressed via μ_2 -receptors.²⁴ However, the opioid receptors involved in the EEG effect in Minto's model may be different from those involved with antitussive action. Therefore, the explanation for the good clinical performance is unclear.

In contrast, recovery profiles such as eye opening time, extubation time, and PACU duration differed between elderly and adult patients in the present study. Although the clinical significance of the prolongation of recovery in the elderly group was relatively minor, it should be treated with caution to some extent. This difference between the elderly and adult patients may be due to several reasons. First, the reduced predictive clinical performance of Minto's model of remifentanyl TCI on recovery profiles. As mentioned earlier, Minto's model is based on the EEG effect of remifentanyl;¹⁴ therefore, the influence of age on other clinical variables such as respiration and analgesia may be different. Second, the interpatient variability of remifentanyl was larger in the elderly patient group than in the adult group.¹⁴ Third, sevoflurane may have affected the results because the elimination rate of sevoflurane can be influenced by variations in the respiratory effect of remifentanyl according to age or because the minimal alveolar concentration of sevoflurane for awakening also decreases with age.²⁵ Therefore, further studies are required to establish a definite conclusion on the influence of age on the clinical performance of remifentanyl TCI with regard to recovery profiles.

Hypoventilation <8 breaths/min occurred in one-third of patients and desaturation below 95% in one patient in the elderly group. These adverse events were more frequent in the elderly group, although this difference lacked statistical significance. Remifentanyl produces respiratory depression in a dose-dependent manner.²⁶ Chang et al²⁷ demonstrated that 2 ng/mL remifentanyl is associated with a significant increase in hypoventilation episodes and delayed emergence. The EC95 of remifentanyl for cough suppression during emergence would be more susceptible to respiratory depression. Therefore, when a remifentanyl EC95 is administered, caution is required with regard to potential hypoventilation and desaturation.

This study has a few limitations. First, patient sex differences at the enrollment stage were not accounted for; the proportion of males in this study was 72%. According to the results of Soh et al,²⁸ the effect-site concentration of remifentanyl TCI for antitussive effect is higher in males than in females. Therefore, variations in the dose–response according to sex may have affected this sequential data. Second, the type of surgery was limited to nasal surgery (endoscopic sinus surgery or septoplasty). Based on the differences in the effect-site concentration of remifentanyl in previous studies of a similar design,^{10,27} surgery type is likely to influence the effect-site concentration of remifentanyl. Therefore, the application of the current findings to other types of surgery should be considered carefully.

Conclusion

The effect-site concentration of remifentanyl for preventing cough after nasal surgery (endoscopic sinus surgery or septoplasty) with sevoflurane anesthesia in elderly patients did not differ from that in adult patients. However, delayed awakening and respiratory adverse events may warrant special attention in elderly patients.

Disclosure

The authors report no conflicts of interest in this work.

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