

# Effect of sex differences in remifentanyl requirements for the insertion of a laryngeal mask airway during propofol anesthesia

## A prospective randomized trial

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### Abstract

**Background:** Remifentanyl can improve insertion of a laryngeal mask airway (LMA) during induction with propofol. Recently, it has been suggested that there is a sex difference in opioid requirements for this procedure. The purposes of this study were to determine the effective effect-site concentration (Ce) of remifentanyl for the facilitation of LMA insertion in male and female patients during propofol anesthesia without neuromuscular blockade and to evaluate whether there are sex differences in the Ce of remifentanyl required for successful LMA insertion.

**Methods:** Forty-eight patients (24 male, 24 female) with American Society of Anesthesiologists physical status 1 or 2, aged 20 to 60 years, scheduled for minor orthopedic surgery under general anesthesia were enrolled. Anesthesia was induced by target-controlled infusion (TCI) of propofol and remifentanyl. The target Ce of propofol was 5 µg/mL initially and was reduced to 3.5 µg/mL after loss of consciousness. The Ce of remifentanyl given to each patient was determined by the response of the previously tested patient using 0.5 ng/mL as a step size. The 1st patient was tested at a Ce of 3.0 ng/mL of remifentanyl. Successful LMA insertion was defined as smooth insertion without patient movement or significant resistance to mouth opening.

**Results:** The effective Ce of remifentanyl required for successful LMA insertion on 50% of occasions (effective effect-site concentration for 50% [EC<sub>50</sub>]) as estimated by Dixon method was significantly lower in women (2.18 ± 0.35 ng/mL) than in men (2.82 ± 0.53 ng/mL) ( $P=0.02$ ). Using the isotonic regression method, the effective Ce of remifentanyl required for successful LMA insertion on 95% of occasions (EC<sub>95</sub>) (95% confidence interval [CI]) was significantly lower in women (3.38 [3.0–3.48] ng/mL) than in men (3.94 [3.80–3.98] ng/mL).

**Conclusion:** The Ce of remifentanyl required to facilitate successful LMA insertion is higher during propofol induction by TCI in men than in women. When using remifentanyl for LMA insertion, patient sex should be taken into account for appropriate dosing.

**Abbreviations:** BIS = bispectral index, Ce = effect-site concentration, CI = confidence interval, EC<sub>50</sub> = effective effect-site concentration for 50%, EC<sub>95</sub> = effective effect-site concentration for 95%, LMA = laryngeal mask airway, TCI = target-controlled infusion.

**Keywords:** anesthesia, laryngeal mask airway, pharmacology, remifentanyl

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## 1. Introduction

Insertion of a laryngeal mask airway (LMA) requires adequate anesthesia to facilitate sufficient mouth opening and suppress of airway reflexes to prevent coughing, gagging, and laryngeal spasm. Propofol has been widely used for LMA insertion because it induces anesthesia rapidly and suppresses upper airway reflexes.<sup>[1]</sup> However, it is difficult to provide good anesthetic conditions for LMA insertion without severe cardiovascular depression when induction is done with propofol alone.<sup>[2–4]</sup> The addition of a short-acting opioid, such as remifentanyl, during induction with propofol is one of the options available to reduce the amount of propofol required for LMA insertion, and provides better insertion conditions without hemodynamic instability.<sup>[5–7]</sup> The effective effect-site concentration (Ce) of remifentanyl required in 50% of adults (effective effect-site concentration for 50% [EC<sub>50</sub>]) via target-controlled infusion (TCI) for successful insertion ranges from 1.36 to 2.84 ng/mL in patients receiving a TCI of propofol at a Ce of 3.5 µg/mL without neuromuscular blockade.<sup>[8,9]</sup>

However, the sex of the patient may affect the analgesic effects of opioids, and the requirement for opioids to achieve the same analgesic effects is higher in men than in women.<sup>[10–12]</sup> In addition, the  $C_e$  of remifentanyl for preventing cough during extubation is higher in men than in women.<sup>[13,14]</sup> Accordingly, we hypothesized that the concentrations of remifentanyl required to suppress airway reflexes and aid LMA insertion might be different between men and women.

The purposes of this study were to determine the  $EC_{50}$  of remifentanyl for the facilitation of LMA insertion in male and female patients during propofol anesthesia without neuromuscular blockade and to evaluate whether there are sex differences in the  $EC_{50}$  of remifentanyl upon successful LMA insertion.

## 2. Methods

This study was approved by the Institutional Review Board of Ajou University Hospital (Ref: MED-OBS-14-325) and registered at <http://cris.nih.go.kr> (REF: KCT0001287). Written informed consent was obtained from each all patients. Forty-eight male or female patients aged 20 to 60 years with American Society of Anesthesiologists physical status I or II and undergoing minor elective orthopedic surgery were enrolled in the study. Patients with signs of difficult intubation, an upper respiratory infection in the previous 2 weeks, gastro-esophageal reflux, history of cardiac, pulmonary, or renal disease, current smoking, a body mass index more than 30 kg/m<sup>2</sup>, and consumption of analgesic medications were excluded from the study.

All patients were premedicated intravenously with glycopyrrolate 0.004 mg/kg before induction of anesthesia. No sedative premedication was given before surgery. Electrocardiogram, peripheral oxygen saturation, noninvasive arterial pressure, and end-tidal CO<sub>2</sub> concentration were monitored every 1 to 5 minutes. The depth of anesthesia was monitored using a bispectral index (BIS) monitor (BIS VISTA™ monitor, 4 electrode sensor; Aspect Medical Systems, Norwood, MA).

All patients were preoxygenated using 100% oxygen with a normal tidal volume for 3 minutes. After intravenous administration of lidocaine 30 mg, induction of anesthesia was performed with a TCI of propofol at a  $C_e$  of 5 μg/mL and remifentanyl at the predetermined  $C_e$ . The  $C_e$  of remifentanyl used for each patient was determined according to the response of the previously tested patient, using the modified Dixon up-and-down method<sup>[15]</sup> (step size 0.5 ng/mL). The 1st patient received a remifentanyl  $C_e$  of 3.0 ng/mL. For the effect-site TCI of propofol and remifentanyl, a 2-channel TCI pump (Orchestra®; Fresenius Vial, Brezins, France) was used. The Marsh and Minto pharmacokinetic models, respectively, were used to calculate the target  $C_e$  for propofol and for remifentanyl. After loss of consciousness, the  $C_e$  of propofol was reduced to 3.5 μg/mL and the patient's lungs were manually ventilated with 100% oxygen through a face mask. A muscle relaxant was not used.

Six minutes after administration of propofol and remifentanyl, an LMA Supreme (Laryngeal Mask Company Limited, Singapore) was inserted (size 3 for women; size 4 for men) by an experienced anesthesiologist according to the manufacturer's recommendations. The anesthesiologist who performed or evaluated the conditions of insertion was unaware of the dose of remifentanyl used.

The response of the patients to LMA insertion was classified by the blinded investigator as either a failure or a success. Failure was defined as major movement of the body or limbs, 2 or more coughs, gags within 1 minute of insertion of the LMA. Also,

significant resistance to mouth opening (Muzi score<sup>[16]</sup> >2; 1 = fully relaxed, 2 = mild resistance, 3 = resistance but could be opened, and 4 = resistance requiring further doses of propofol) was defined as a failed insertion. Success was defined as the absence of the above-mentioned reactions.<sup>[17]</sup> If the LMA insertion failed, further doses of propofol or remifentanyl were given according to the patient's clinical status, and insertion of the LMA was reattempted.

The patient's heart rate, mean arterial pressure, peripheral oxygen saturation, and BIS were recorded at baseline (just before induction), at 3 and 6 minutes after administration of propofol and remifentanyl and 1 minute after insertion of the LMA. Hypotension was defined as a mean arterial pressure <60 mm Hg or a decrease of >30% from baseline that persisted for more than 1 minute, and was treated with a bolus of intravenous ephedrine (4–6 mg). A heart rate <45 beats/minute or a decrease of >30% from baseline lasting more than 1 minute was defined as bradycardia and treated with 0.5 mg of intravenous atropine.

According to previous studies in which the  $EC_{50}$  was estimated by Dixon method, at least 6 failure/success crossover pairs were required.<sup>[7,13]</sup> Simulation studies for the up and down design suggest that at least 20 patients should be included.<sup>[18]</sup> Twenty-four patients of each sex were included in our study to obtain stable estimations.

The statistical analysis was performed using SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL) and R for Windows (version for R 3.0.1). Data are expressed as the mean ± standard deviation or the number (percentage) of patients. The  $EC_{50}$  of the remifentanyl  $C_e$  that enabled successful LMA insertion was determined by calculating the average of the midpoint dose for each independent pair of patients after 7 crossover points were obtained in each group, and the mean  $EC_{50}$  values of each group were compared using a *t* test. For backup analysis, the data were also subjected to isotonic regression estimators for calculation of the effective  $C_e$  on 95% of occasions (effective effect-site concentration for 95% [ $EC_{95}$ ]) and the 95% confidence interval (CI).<sup>[19]</sup> An adjusted response probability was calculated by the pooled adjacent-violators algorithm, and the CI was estimated by a bootstrapping approach.<sup>[18]</sup> Hemodynamic and BIS changes were compared by repeated measures analysis of variance. All *P*-values <0.05 were considered to be statistically significant.

## 3. Results

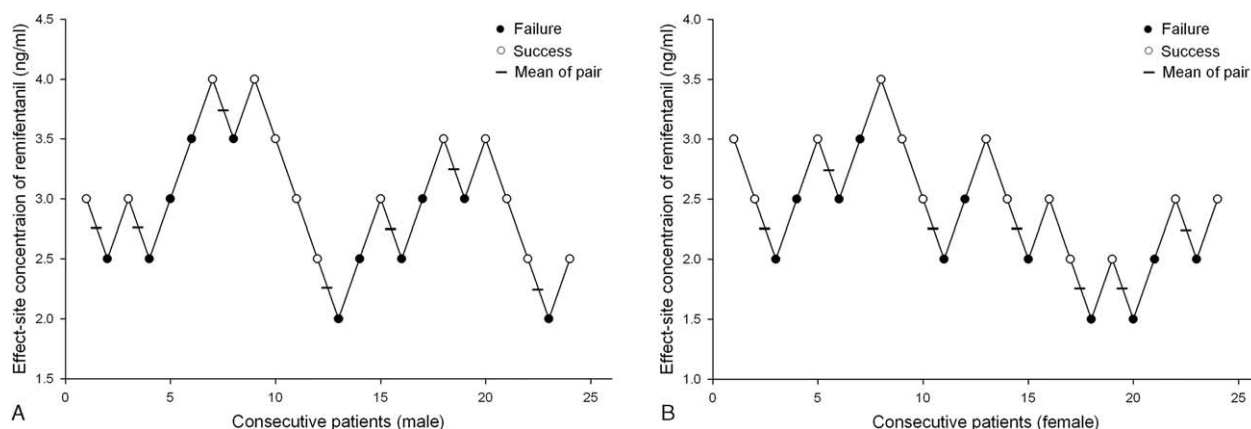
Forty-eight patients (24 male, 24 female) were enrolled. The patients' characteristics are shown in Table 1. Age and American Society of Anesthesiologists physical status classification were not different between the sexes. However, height, weight, and lean body mass were significantly lower in women.

The sequences for success and failure of LMA insertion in the 2 groups are shown in Fig. 1. The  $EC_{50}$  of the remifentanyl  $C_e$  for

**Table 1**  
Patient characteristics.

	Male (n=24)	Female (n=24)	<i>P</i>
Age, years	41.67 ± 12.38	43.62 ± 9.28	0.54
Height, cm	172.13 ± 5.96	159.17 ± 4.10	<0.001
Weight, kg	72.58 ± 9.49	57.75 ± 8.95	<0.001
Estimated lean body mass	52.70 ± 4.40	40.33 ± 3.84	<0.001
ASA physical status (I/II)	22/2	21/3	0.65

Values are presented as the mean ± standard deviation or numbers. ASA = American Society of Anesthesiologists.



**Figure 1.** Assessment of success or failure of LMA insertion under a predetermined concentration of remifentanyl using the Dixon up-and-down method in 24 consecutive male patients (A) and 24 consecutive female patients (B). Horizontal bars represent crossover mid points (success to failure). The EC<sub>50</sub> of remifentanyl for successful LMA insertion in the male group and the group was 2.82±0.53 and 2.18±0.35 ng/mL, respectively. EC<sub>50</sub>=effective effect-site concentration for 50%, LMA=laryngeal mask airway.

successful LMA insertion estimated by Dixon method in the women (2.18±0.35 ng/mL) was significantly lower than in the men (2.82±0.53 ng/mL) (*P*=0.02).

Using the isotonic regression method and CI calculated by the bootstrapping approach, the EC<sub>95</sub> (95% CI) of remifentanyl Ce in the women [3.38 (3.0–3.48) ng/mL] was significantly lower than in the men [3.94 (3.80–3.98) ng/mL].

The hemodynamic data during induction of anesthesia are shown in Table 2. The hemodynamic and BIS data were not significantly different between the sexes over time.

**4. Discussion**

Using the modified Dixon method, the present study demonstrates that the remifentanyl Ce required for successful LMA insertion in patients on 50% of occasions was significantly higher in men (2.82±0.53 ng/mL) than in women (2.18±0.35 ng/mL) during induction with propofol TCI without neuromuscular blockade.

Interest in differences between the sexes with regard to the pharmacokinetics and pharmacodynamics of anesthetics is growing; of the many anesthetic agents available, opioids are the most commonly associated with sex differences.<sup>[10–12]</sup> To date, there have been no reports of a sex difference in the remifentanyl requirement for insertion of a supraglottic airway during propofol induction. In our study, the EC<sub>50</sub> and EC<sub>95</sub> of remifentanyl required for successful LMA insertion were both

significantly higher in men than in women during propofol TCI induction.

There are some possible reasons for our results. First, there is a sex difference in sensitivity to opioid receptor agonists. Women have greater sensitivity to μ-opioid receptors than men, which leads to sex differences in the response to pain and analgesia.<sup>[20]</sup> Second, there is a likely to be a sex difference in suppression of the cough reflex or airway reactivity by opioids, which is one of the most important factors determining successful insertion of an LMA without neuromuscular blockade. A previous report on the remifentanyl requirement for suppressing cough during emergence from anesthesia reported that the EC<sub>50</sub> of remifentanyl for suppressing cough was almost twice as high in men than in women.<sup>[14]</sup> The authors suggested that during emergence from anesthesia, the anesthetic concentration for cough suppression may differ between the sexes under similar clinical conditions. In addition, in an experimental study, male sex hormones promoted the reflex airway response to cholinergic stimulation, which indicates that there could be a sex disparity in airway responsiveness.<sup>[21]</sup> Third, there is sex difference in the activity of nonspecific esterase. Remifentanyl is inactivated by ester hydrolysis. Because esterase activity has been reported to be regulated by both prenatal and postnatal exposure to endogenous sex steroids,<sup>[22]</sup> a sex difference in esterase activity might have influenced our results. The specific esterase enzymes responsible for metabolizing remifentanyl have not been identified. Remifentanyl esterase activity is present in red cells but not in

**Table 2**  
**Hemodynamic profiles and BISs during laryngeal mask airway insertion.**

	Sex	Baseline	3minute after induction	6 minute after induction	1 minute after LMA insertion
MBP, mmHg	Male	96.7±22.7	77.2±13.1	71.2±10.6	75.3±9.5
	Female	100.7±14.4	81.2±14.7	73.3±11.9	82.0±15.8
HR, beats/minute	Male	70.0±14.4	70.0±13.1	71.2±10.6	72.3±16.0
	Female	80.5±14.3	73.0±11.4	70.7±11.4	72.0±16.0
SpO <sub>2</sub> , %	Male	98.2±1.2	98.6±1.1	99.4±0.5	99.3±0.5
	Female	98.6±1.1	99.8±0.4	99.5±0.5	99.6±0.5
BIS	Male	96.3±2.2	57.5±14.3	54.4±7.1	53.2±9.0
	Female	96.6±1.0	58.4±11.4	56.3±8.9	56.3±14.0

Values are showed as the mean±standard deviation. BIS=bispectral index, HR=heart rate, MAP=mean arterial pressure, SpO<sub>2</sub>=peripheral oxygen saturation.

plasma.<sup>[23]</sup> Red cell esterase activity probably does not account for the rapidity of remifentanil clearance, suggesting that tissue esterase is significantly involved.<sup>[23]</sup> More research on the effect of sex hormones on the metabolism of remifentanil might be needed. Furthermore, because a sex-specific effect on enzyme systems is associated with drug metabolism, this effect might be more important during emergence from anesthesia than during induction of anesthesia or insertion of an LMA.

In the present study, the Minto pharmacokinetic model was used for TCI of remifentanil. Age and lean body mass are significant covariates in the pharmacokinetics of remifentanil, but sex is not in the Minto model.<sup>[24]</sup> No sex difference in electroencephalographic or pharmacokinetic variables has been observed.<sup>[24]</sup> In the present study, height, weight, and lean body mass of women, in which could influence the pharmacokinetic variables, were lower than men. However, because the remifentanil Ce was calculated and adjusted by these covariates in the Minto model, the effect of differences in demographic data on our results are likely to be small.

The present study calculated the EC<sub>95</sub>, which has clinical significance, using isotonic regression and showed a statistically significant difference in EC<sub>95</sub> (95% CI) for remifentanil between men (3.94 [3.80–3.98] ng/mL) and women (3.38 [3.0–3.48] ng/mL). Our results are comparable with those of a recent clinical study in women<sup>[17]</sup> that reported the EC<sub>95</sub> (95% CI) of remifentanil TCI to be 3.35 (2.58–3.48) ng/mL during propofol TCI induction (Ce 5 µg/mL). Previous studies have investigated the optimal remifentanil Ce for insertion of an LMA during induction with propofol TCI. Kim et al<sup>[18]</sup> reported that the EC<sub>95</sub> of remifentanil for conventional LMA insertion was 3.79 ng/mL during induction with propofol TCI at 3.5 µg/mL. Another study reported that the EC<sub>95</sub> of remifentanil for insertion of an LMA Softseal was 2.43 ng/mL with a propofol Ce of 3.5 µg/mL.<sup>[19]</sup> These differences could be explained by differences in study design, such as the use of sedative premedication, different performance of LMA subtypes, or a different male to female ratio.

There are several limitations in our study. First, the estimated remifentanil concentration was limited to a fixed concentration of propofol. Propofol reduces remifentanil requirements for suppression of airway stimulation in a synergistic manner.<sup>[25]</sup> Second, we cannot exclude the influence of propofol on the required remifentanil Ce. In the present study, the Marsh pharmacokinetic model was used for the propofol TCI. When applying the Marsh model, the estimated concentration of propofol is less accurate in men than in women.<sup>[26]</sup> Different concentration of propofol in men and women may affect LMA insertion, so measurement of the actual concentration of propofol may be needed in this type of study. Therefore, further research might be needed to elucidate the sex difference in anesthetic requirements for remifentanil in relation to the pharmacokinetics or concentration of propofol. Third, the concentration of remifentanil used was calculated using a pharmacokinetic model, not an actual measurement obtained from patient blood sampling. However, the Minto pharmacokinetic model for remifentanil has been commonly used with acceptable levels of bias and accuracy in the clinical setting.<sup>[27]</sup> Thus, this predicted remifentanil EC can be used reliably in clinical practice. Finally, we have also presented the EC<sub>95</sub> of remifentanil. However, an EC<sub>95</sub> calculated in an up-and-down sequential allocation design focusing on the EC<sub>50</sub> cannot be a reliable value.<sup>[18]</sup> Therefore, the EC<sub>95</sub> of remifentanil for LMA insertion estimated in this study cannot be applied in clinical practice and should be confirmed in an appropriately designed study for determining the EC<sub>95</sub>.<sup>[18,19]</sup>

In conclusion, the required remifentanil Ce at which successful LMA insertion is possible in 50% of men and women was 2.82 and 2.18 ng/mL, respectively, during a propofol TCI without neuromuscular blockade using the modified Dixon up-and-down method. The remifentanil Ce required to facilitate successful LMA insertion during propofol TCI induction is higher in men than in women. When using remifentanil for LMA insertion, patient sex should be considered for appropriate dosing.

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