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Low dose of fentanyl reduces predicted effect-site concentration of propofol for flexible laryngeal mask airway insertion

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Abstract
Purpose. In contrast to reports on the classical laryngeal mask airway (classical LMA; CLMA), no report has calculated the 50% and 95% effect-site concentrations (EC_{50} and EC_{95}, respectively) of propofol required for flexible LMA (FLMA) insertion. This study was designed to determine the EC_{50} and EC_{95} of propofol for FLMA insertion, using probit analysis, and to investigate whether supplemental 0.25 $\mu g \cdot kg^{-1}$ fentanyl decreased these concentrations.
Methods. Fifty-nine unpremedicated patients who were scheduled for elective minor oral surgery were randomly allocated to a saline-propofol group (S-P group; $n = 30$) or a fentanyl-propofol group (F-P group; $n = 29$). Each group was further divided into four subgroups, in which the propofol EC for FLMA insertion was set at 2.5, 3.0, 3.5, and 4.0 $\mu g \cdot ml^{-1}$, respectively, in the S-P group and 1.8, 2.0, 2.5, and 3.0 $\mu g \cdot ml^{-1}$, respectively, in the F-P group,. The experiment was assessed as "successful" when FLMA insertion within 1 min was possible.
Results. The EC_{50} and EC_{95} in the S-P group were 3.29 (95% confidence interval [CI], 2.83–3.93) and 4.73 (95% CI, 3.94–12.22) $\mu g \cdot ml^{-1}$, and those in the F-P group were 2.13 (95% CI, 1.42–2.60) and 3.54 95% CI, (2.78–34.78) $\mu g \cdot ml^{-1}$, respectively. The EC_{50} in the F-P group was significantly lower than that in the S-P group. There were no significant differences in bispectral index (BIS), hemodynamic variables, respiratory rate, and arterial oxygen saturation (S_{PO_2}) between the S-P and F-P groups.
Conclusion. The propofol EC_{50} for FLMA insertion was decreased by supplemental 0.25 $\mu g \cdot kg^{-1}$ fentanyl without BIS, hemodynamic, or respiratory depression.

Key words Flexible laryngeal mask airway · Propofol · Fentanyl · Bispectral index

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Introduction

The laryngeal mask airway (LMA) has become a common device used for airway management during anesthesia for relatively short procedures such as adenotonsillectomy, laser pharyngoplasty, and minor oral surgery [1]. The flexible laryngeal mask airway (reinforced LMA; FLMA) has been developed as a modification of the standard-type LMA (classical-type LMA; CLMA). Although the cuff portion of the FLMA is identical to that of the CLMA, the FLMA has a long narrow nonridged flexometallic tube. This flexible structure does not interfere with the surgical field in the oral region.

In a previous report, the predicted propofol effect-site concentrations (ECs) required to prevent movement of the body or limbs in 50% of patients (EC_{50}) at the insertion of various types of LMA were determined and compared with each other [2]. The results of that report showed there were significant differences among propofol EC_{50s} for Proseal (LMA, San Diego, CA, USA), Fastrach (LMA, San Diego, CA, USA), and CLMA insertion. However, nothing was written about the FLMA in that report. Another report [1] showed the ease of insertion for FLMA was similar to that of the CLMA; however, the authors compared these LMAs based only on the difficulty of the insertion technique, but not on the physiological stress of insertion. The EC_{50} required for FLMA insertion has not yet been examined. We expected that the physiological stress of FLMA insertion would be less than that of other types of LMA, and we hypothesized that it could be possible to insert the FLMA with a lower EC of propofol.

In most reports on propofol EC for LMA insertion, the 95% EC (EC_{95}) was not investigated because of the methodology used. Casati et al. [3] reported the target plasma concentration of propofol for successful LMA insertion in 95% of patients was at least 6 $\mu g \cdot ml^{-1}$. However, their result was obtained by increasing the

propofol concentration by 0.5-μg·ml^{-1} steps until the patient did not show responses for LMA insertion. Higher values may have been obtained by this method because of its one-way step-up condition. Although regression analysis can overcome these problems, there is no report on the propofol EC_{95} for LMA insertion calculated by using regression analysis.

Fentanyl 0.5, 1, and 2 μg·kg^{-1} combined with propofol decreased the EC_{50} of propofol for CLMA insertion [4]. The authors of that study concluded that supplemental 0.5 μg·kg^{-1} fentanyl was sufficient to decrease the predicted EC_{50} with minimal respiratory depression. In that report, however, the effect of a lower dose of fentanyl than 0.5 μg·kg^{-1} was not examined. We expected that an 0.25-μg·kg^{-1} fentanyl supplement would be useful for the insertion of an FLMA without respiratory depression, because it was reported that 0.25 μg·kg^{-1} fentanyl is the lowest dose required to produce an analgesic effect [5].

The aim of the present study was to investigate the predicted propofol EC_{50} and EC_{95} with or without supplemental 0.25 μg·kg^{-1} of fentanyl for FLMA insertion and to examine the effect of a low dose of fentanyl.

Patients and methods

After obtaining approval from the clinical research ethics committee of Tokyo Dental College (no.143), we obtained written informed consent from 59 patients. All patients were classified as American Society of Anesthesiologists (ASA) physical status (PS) I or II, and were aged 18–50 years and scheduled for minor oral surgery, such as the removal of plates of the mandible, in which the use of an FLMA was indicated. Patients were excluded if they were significantly obese (body mass index >35 kg·m^{-2}), smoked more than 40 cigarettes per day, or were taking analgesic medication. We also excluded patients with a known difficult airway (Mallampati grade III, IV) or a mouth opening less than 2.5 cm. In addition, patients who were at high risk of aspiration; for example, patients who had a history of aspiration pneumonia or cerebral palsy, or those with known allergies to propofol or fentanyl were excluded. All patients received ranitidine 150 mg orally 90 min before arriving at the operating room. None of them were premedicated with an opiate or sedative agent. Patients were randomly allocated to two groups; a saline-propofol group (S-P group; n = 30) and a fentanyl-propofol group (F-P group; n = 29). Each group was further randomly divided into four subgroups. A table of random numbers was used for randomization. The target concentrations of propofol in the subgroups, determined based on a pilot study, were: 2.5, 3.0, 3.5, and 4.0 μg·ml^{-1}, respectively, in the S-P group and 1.8, 2.0, 2.5, 3.0 μg·ml^{-1}, respectively, in the F-P group.

After the patient arrived at the operating room, a 20-gauge venous cannula was inserted into a left cephalic vein, and acetated Ringer's solution was infused at 100 ml·h^{-1}. Before induction of anesthesia, all patients received pirenzepine 10 mg intravenously. Noninvasive arterial pressure (systolic blood pressure, SBP; diastolic BP, DBP), electrocardiogram, heart rate (HR), arterial oxygen saturation (Sp_{O_2}), and respiratory rate (RR) were monitored using a multi-analyzer (Cardioscap/5; Datex-Ohmeda, Teollisuuskatu, Helsinki, Finland). The depth of sedation was evaluated with a bispectral index (BIS) monitor (A-1050; Aspect Medical Systems, Newton, MA, USA). These measurements were recorded before induction, immediately prior to the injection of saline or fentanyl, and immediately prior to the insertion of the FLMA. Propofol was administered by a computer-assisted continuous infusion technique with 100% oxygen via a facial mask. An anesthesia syringe pump (TE-371; Terumo, Tokyo, Japan) incorporating target-controlled infusion (TCI) software (standard Diprifusor, AstraZeneca Pharmaceuticals, Cheshire, UK) was used throughout this study.

Three of the authors participated in this experiment in the operating room. The first person was a dental anesthesiologist who set the TCI target concentration, administered saline or fentanyl, and worked as a timekeeper. The second person, also a dental anesthesiologist, who was an expert in FLMA insertion, inserted the FLMA in all of the patients in this study. The third person judged the "success" or "failure" of the FLMA insertion. The latter two persons had not been informed about the propofol concentration and whether or not fentanyl was injected. The first dental anesthesiologist started the infusion, and 11 min after the equilibrium period of the predetermined propofol target and effect site, injected either saline or fentanyl 0.25 μg·kg^{-1}. Four minutes (the time at which the peak EC of fentanyl would be attained [6]) after the saline or fentanyl injection, FLMA insertion was attempted. If the Sp_{O_2} became less than 90% because of airway obstruction, the patient's jaw was lifted to maintain the airway and the experiment was continued. Positive pressure ventilation with 100% oxygen with a facemask was performed if there was no recovery of Sp_{O_2} or if the patient became apneic.

The FLMA (size 3 or 4) was inserted using the "standard" (front-to-front) method with the airway cuff inflated with 10 ml air. One experiment was performed for each patient. The decision of "failure" was made when FLMA insertion within 1 min was impossible because of the patient's movement, such as trismus, coughing, and gagging. It was judged as a "success" when the FLMA was inserted smoothly within 1 min even though minor movement, such as movement of fingers, was observed in the patient. In addition, patients

Table 1. Patients' characteristics

	S-P group				F-P group			
Group	2.5	3	3.5	4 ($\mu g \cdot ml^{-1}$)	1.8	2	2.5	3 ($\mu g \cdot ml^{-1}$)
Number (n)	7	7	7	7	7	7	7	7
Male/Female	2/5	2/5	2/5	2/5	3/4	2/5	4/3	3/4
Age (years)	28.4 (8.9)	27.9 (6.5)	32.9 (9.6)	28.0 (9.1)	24.0 (6.6)	28.4 (9.9)	35.3 (9.6)	25.3 (5.8)
Weight (kg)	55.6 (12.4)	57.6 (11.7)	59.9 (12.5)	56.4 (6.2)	52.6 (7.4)	55.9 (8.3)	60.7 (8.9)	58.4 (11.0)
Height (cm)	160.4 (9.2)	160.6 (12.3)	164.3 (10.5)	164.1 (7.5)	157.9 (9.8)	162.9 (6.0)	167.6 (8.5)	165.6 (8.9)

Data values are presented as means (SD)

were excluded if the insertion was considered impossible because they were still conscious immediately before the insertion. For the "failure" patients, we finished the experiment and inserted an FLMA after increasing the propofol concentration.

The EC_{50} and EC_{95} values and their 95% confidence interval (CI) ranges were calculated by probit analysis. If there was no overlap between two 95% CIs of both groups, the difference was considered to be significant. Probit analysis and parallelism test between two regression lines were performed using SPSS II software version 11.0 for Windows (SPSS, Chicago, IL, USA). Data for patients' characteristics (age, weight, height) were analyzed by nonrepeated measures analysis of variance (ANOVA). If a significant difference was detected, this analysis was followed by the Student-Newman-Keuls test (SNK test). Differences in sex ratios were compared with the χ^2 test. Changes in BIS, BP, HR, Sp_{O_2}, and RR between preinduction and preinsertion were analyzed by the Wilcoxon signed rank sum test. The differences in hemodynamic and respiratory data among groups at preinsertion were compared by the Kruskal Wallis H-test followed by the Mann-Whitney U-test with Bonferroni correction. Changes in BIS values between immediately before fentanyl administration and preinsertion were compared with the Wilcoxon signed rank sum test. P values of less than 0.05 were considered statistically significant.

Results

Three patients (2 in the S-P group and 1 in the F-P group) were excluded because they were conscious immediately before the FLMA insertion. Data from 56 patients (S-P group, $n = 28$; F-P group, $n = 28$) were used for analysis. Characteristic data are shown in Table 1. There were no differences in sex ratios, age, height, and weight among the subgroups. The relationship between propofol EC and the probability of "success" of FLMA insertion is illustrated in Fig. 1. The EC_{50} and EC_{95} of the S-P group were 3.29 (95% CI, 2.83–3.93) and 4.73 (95% CI, 3.94–12.22) $\mu g \cdot ml^{-1}$, respectively, and those of the F-P group were 2.13 (95% CI, 1.42–2.60) and 3.54 (95% CI, 2.78–34.78) $\mu g \cdot ml^{-1}$, respectively. The EC_{50} value of the F-P group was significantly lower than that of the S-P group. The EC_{95} value of the F-P group decreased to about 75% of that of the S-P group, though these two values were not significantly different. The probit regression line of propofol was shifted leftwards by combining fentanyl with propofol. There was no significant difference in the slopes of the probit regression lines between the S-P and F-P groups.

Each parameter at preinduction (a) and preinsertion (b) is shown in Table 2. BP and BIS values at preinsertion were significantly lower than those at preinduction, while HR, Sp_{O_2}, and RR did not show significant differences. There were no differences in these parameters among the subgroups at preinsertion. In addition, there were no differences in these parameters at 2.5 or 3.0 $\mu g \cdot ml^{-1}$ between the S-P and the F-P groups. Comparisons of BIS values between immediately before fentanyl administration and at preinsertion in the F-P group are shown in Fig. 2. BIS values were not changed by fentanyl supplement.

No life-threatening complication occurred during the perioperative period. At postoperative interviews, no patient recalled any event during FLMA insertion or surgery.

Discussion

This study demonstrated that the EC_{50} level of propofol needed for FLMA insertion was reduced by fentanyl supplement at 0.25 $\mu g \cdot kg^{-1}$ without risk of hypotension or respiratory depression. The concentration-response curve of propofol was shifted leftwards by the addition of the low dose of fentanyl. In addition, this dose of fentanyl did not affect BIS values.

Propofol has depressant effects on the upper airway reflex [7], which can provide a suitable condition for LMA insertion [8]. The plasma concentration of propofol required for LMA insertion may be different among various types of LMA. It was reported that the 50% predicted plasma concentrations of propofol (Cp_{50s}) for

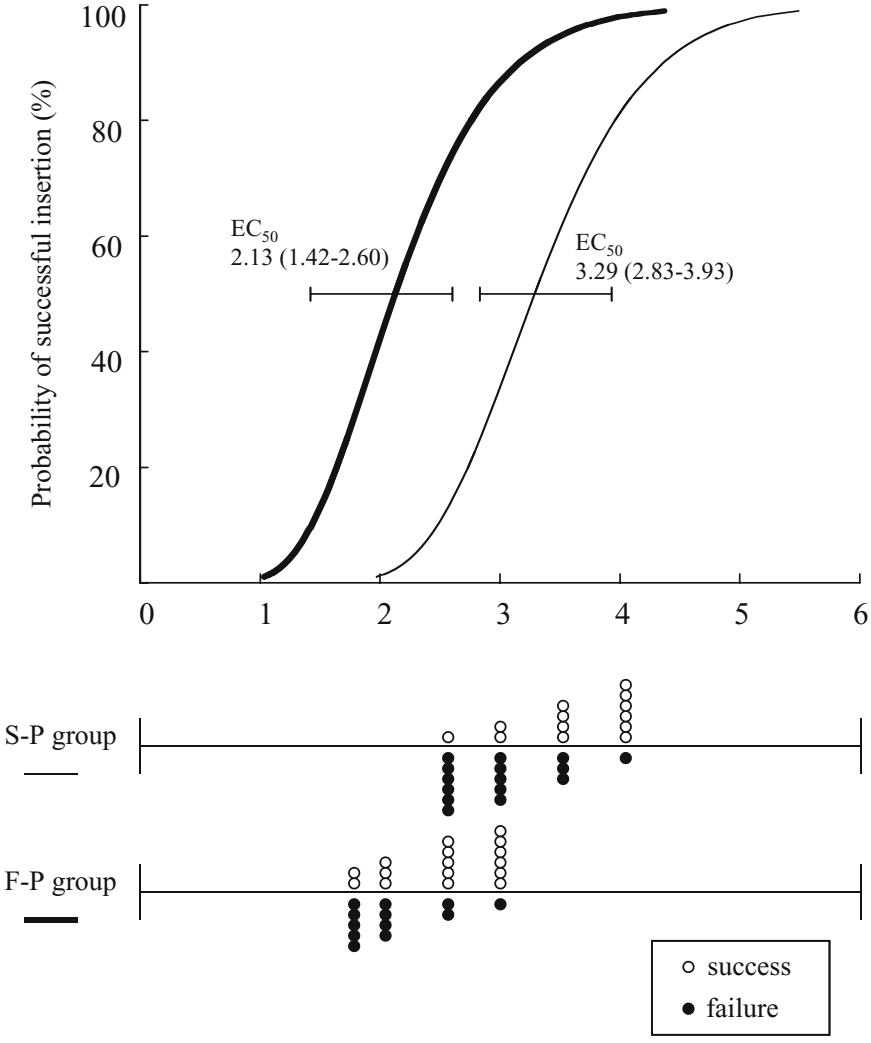

Fig. 1. Concentration-response curves for the insertion of a flexible laryngeal mask airway (FLMA) in the saline-propofol group (*S-P group; thin curve*) and FLMA group (*F-P group; thick curve*). *Each bar* represents the 95% confidence interval of the effect-site concentration required to prevent movement of the body or limbs in 50% of patients (EC_{50}). The concentration-response curve of propofol was shifted to the leftward in parallel by combining propofol with low-dose fentanyl

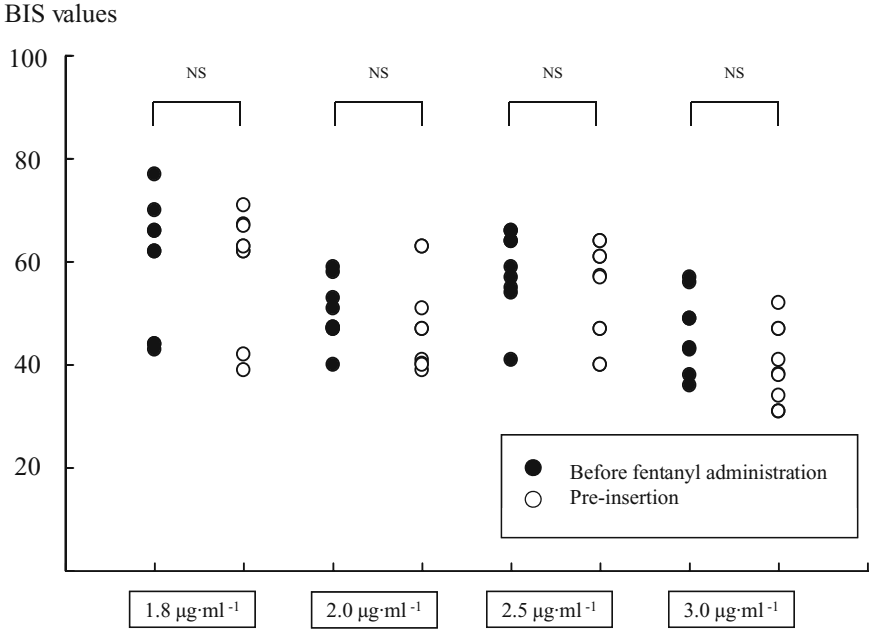

Fig. 2. Comparison of bispectral index (*BIS*) values in the F-P group between before fentanyl injection and immediately before the FLMA insertion. No significant changes were produced in BIS values by 0.25-μg·ml^{-1} fentanyl supplement. *NS*, Not significant

Table 2. Changes in cardiorespiratory variables and BIS values at different effect-site concentrations of propofol

	S-P group				F-P group			
Group	2.5	3	3.5	4 (μg·ml^{-1})	1.8	2	2.5	3 (μg·ml^{-1})
BIS value								
a	95.9 (2.1)	97.4 (0.5)	97.0 (1.0)	97.2 (0.8)	96.9 (1.4)	96.3 (2.0)	96.9 (1.3)	96.7 (1.6)
b	45.7 (8.3)*	41.3 (10.1)*	39.0 (5.2)*	35.9 (3.9)*	58.7 (12.8)*	45.9 (8.8)*	52.3 (9.9)*	40.1 (7.3)*
SBP (mmHg)								
a	112 (8.4)	120 (19.8)	105 (9.4)	116 (5.2)	121 (11.2)	113 (14.0)	121 (11.0)	112 (6.8)
b	94 (7.3)*	99 (10.6)*	91 (7.2)*	94 (7.7)*	88 (20.2)*	97 (7.7)*	98 (12.0)	93 (5.0)
DBP (mmHg)								
a	73 (11.0)	66 (15.3)	61 (8.3)	74 (6.4)	70 (11.8)	66 (8.2)	70 (12.0)	62 (6.0)
b	52 (6.6)*	57 (11.4)*	49 (12.4)*	53 (10.2)*	58 (15.7)*	54 (5.3)*	53 (8.4)*	50 (6.2)*
HR (min^{-1})								
a	59 (5.4)	64 (14.0)	54 (6.5)	64 (6.9)	56 (11.1)	57 (12.6)	56 (11.0)	65 (8.1)
b	58 (12.0)	61 (12.0)	62 (9.5)	63 (8.4)	58 (15.7)	54 (5.3)	53 (8.4)	50 (6.2)
Sp_{O_2} (%)								
a	98.9 (1.5)	99.4 (0.8)	98.3 (1.0)	98.7 (0.8)	98.6 (1.0)	98.9 (0.9)	98.9 (1.0)	99.1 (1.2)
b	98.4 (1.8)	99.3 (1.0)	99.3 (0.8)	99.3 (0.4)	99.4 (0.8)	98.7 (1.0)	98.9 (1.1)	99.1 (0.9)
RR (min^{-1})								
a	18.0 (4.0)	15.7 (4.9)	17.0 (3.2)	17.0 (5.7)	19.7 (4.7)	17.9 (3.5)	16.7 (3.2)	17.9 (3.5)
b	15.7 (3.0)	18.0 (2.5)	16.3 (3.9)	17.3 (4.6)	16.0 (3.8)	14.9 (3.0)	14.1 (4.7)	15.7 (3.1)

Data values are presented as means (SD)
a, preinduction; b, preinsertion; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate
* $P < 0.05$ compared with preinduction

CLMA, Fastrach LMA, and ProSeal LMA insertion were 3.2 ± 0.34, 4.0 ± 0.22, and 4.9 ± 0.20 μg·ml^{-1}, respectively [2]. Other previous studies had reported that EC_{50}s for CLMA insertion were 4.3 ± 0.8 μg·ml^{-1} [3] and 3.25 ± 0.25 μg·ml^{-1} [4]. In our result, the propofol EC_{50} for FLMA insertion was similar to that for the CLMA reported by Kodaka et al. [4].

In our study, the induction and maintenance of propofol anesthesia were performed with a TCI system using the Diprifusor. This experimental condition was similar to that in previous studies [2–4]. However, our study was different from these previous studies in two aspects.

First, the equilibrium period between plasma and effect-site concentration and the attempt at LMA insertion (elapsed time) in our study was longer than those in the previous studies. The elapsed time to achieve a steady-state concentration of propofol at the effect site could affect the success rate of LMA insertion. Equilibrium of the effect site with blood concentration takes 4–5 times the k_{eo} half-life [$T_{1/2}(k_{eo})$], where $T_{1/2}(k_{eo}) = 0.693 / k_{eo}$ [9]. The constant k_{eo} describes the removal of drug from the effect site. The pharmacokinetic model with the Diprifusor uses the k_{eo} value of 0.286 min^{-1} [10]. We accordingly kept the effect-site concentration (EC) for 15 min before FLMA insertion in both our groups.

Second, the method of EC_{50} calculation in our study was different from that used in the previous studies. In our study, EC_{50} and EC_{95} were derived from the concentration-response curve for propofol with and without fentanyl. The EC_{95} value should be applicable to the clinical situation. However the EC_{95} cannot be obtained by Dixon's up-and-down method (stair-cast method) [11], which was used in the previous studies [2,4], because this method is basically designed to detect the 50% effect dose with fewer samples. On the other hand, probit analysis also has some problems. In our results, the 95% CIs were too large in both the S-P group and the F-P group. Therefore, there was no difference between these two groups. However, the fact that supplemental 0.25 μg·kg^{-1} fentanyl decreased the propofol EC_{95} value for FLMA insertion by 25% is useful information in the clinical setting. The width of the 95% CI depends on the number of patients and the ranges of stepwise propofol ECs predetermined for each subgroup. It is important to improve these two factors to obtain a narrower CI range.

It has been demonstrated that fentanyl reduces the propofol EC_{50} for various stimuli, such as verbal command [12], skin incision [12,13], peritoneal incision [14], abdominal wall retraction [14], laryngoscopy [15], tracheal intubation [15], and CLMA insertion [4]. A study of the requirement of propofol combined with fentanyl 0.5, 1.0, and 2.0 μg·kg^{-1} showed that the EC_{50} values for CLMA insertion were 2.06 ± 0.55, 1.69 ± 0.38, and 1.50 ± 0.54 μg·ml^{-1}, respectively [4]. Although all of these values were significantly lower compared with that of propofol alone, there were no significant differences among these three values. The EC_{50} in the present study was 2.13 μg·ml^{-1} when supplemental 0.25 μg·kg^{-1}

fentanyl was used. This value is comparable to the value of 2.06 $\mu g \cdot ml^{-1}$ when supplemental 0.5 $\mu g \cdot kg^{-1}$ fentanyl was used [4].

Our study demonstrated that the probit regression line of propofol was shifted leftwards by combining propofol with 0.25 $\mu g \cdot kg^{-1}$ fentanyl, although no additional changes were produced in BIS values by the fentanyl supplement. It has been reported that propofol has an inhibitory effect by acting on gamma-aminobutyric acid (GABA) receptors [16] and that fentanyl has an antinoxious effect mediated by μ and κ opiate receptors in the central nervous system [17,18]. Smith and colleagues [12] suggested that the interaction between fentanyl and propofol in inhibiting the response to skin incision was more remarkable than the interaction in inducing loss of consciousness. In a recent report [19], it was shown that remifentanil, a μ-receptor agonist, also had a minimal effect on changes in BIS values during propofol anesthesia, without producing any stimulation. On the other hand, it was demonstrated that a cumulative dose of 200 μg fentanyl supressed airway reflexes (including expiration reflex, spasmodic panting, and cough reflex) [20]. The authors of that study [20] speculated that the mechanism of this depression could be that activation of the opiate system could modify the central respiratory network, thereby causing the dose-related depression of airway reflexes. These previous reports suggest fentanyl has an inhibitory effect on upper airway reflexes, although the effect is not reflected in BIS values. Therefore, we suppose that the combination of propofol and fentanyl interacts to inhibit noxious upper airway reflexes, although the fentanyl dose in our study was much lower than that in previous reports.

Our results are not enough to determine the mechanism of interaction between propofol and fentanyl. Further studies, such as response surface analysis [21], are warranted to examine the potential interaction of propofol and fentanyl for LMA insertion.

In conclusion, the propofol EC_{50} for FLMA insertion was decreased by supplemental 0.25 $\mu g \cdot kg^{-1}$ fentanyl, without causing BIS, hemodynamic, or respiratory depression.

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