Optimal remifentanyl dose for laryngeal mask airway insertion when co-administered with a single standard dose of propofol

Dose optimale de rémifentanyl pour l'insertion d'un masque laryngé lors de la co-administration d'une dose standard unique de propofol

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Abstract

Purpose This dose-response study aimed to determine the optimal dose of remifentanyl combined with propofol 2.5 mg·kg⁻¹ iv in order to achieve excellent conditions for laryngeal mask airway (LMATM) insertion in 95% of adult female patients.

Methods Sixty-eight adult premedicated female patients, American Society of Anesthesiologists (ASA) physical status I and II requiring anesthesia for ambulatory surgery, were randomly allocated to one of four remifentanyl dose groups (0.25, 0.5, 1, or 2 µg·kg⁻¹). Induction of anesthesia was achieved with one of the four blinded doses of remifentanyl infused over 60 sec and simultaneously co-administered with propofol 2.5 mg·kg⁻¹ iv infused over 45 sec. Insertion of the LMA was attempted 150 sec after the beginning of the induction sequence. Insertion conditions were assessed using a six-category score according to resistance to mouth opening and insertion, swallowing, coughing and gagging,

movement, and laryngospasm. A probit analysis was performed to calculate the effective dose for insertion of the LMA in 95% of patients (efficient dose [ED]₉₅). The changes in heart rate (HR) and mean arterial blood pressure (MAP) in response to LMA insertion were recorded and compared as secondary outcome variables.

Results The ED₉₅ of remifentanyl was 1.32 (95% confidence interval [CI] 0.99–2.46) µg·kg⁻¹. Changes in heart rate and mean arterial pressure were modest and similar over time across groups, with maximum decreases in heart rate and mean arterial pressure < 30% each during induction of anesthesia.

Conclusions The required dose of remifentanyl is 1.32 (95% CI 0.99–2.46) µg·kg⁻¹ to achieve excellent LMA insertion conditions in 95% of patients when co-administered with propofol 2.5 mg·kg⁻¹ in healthy premedicated female patients undergoing elective ambulatory surgery.

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Résumé

Objectif L'objectif de cette étude de dose-réponse était de déterminer la dose optimale de rémifentanyl lors de l'administration conjointe de propofol 2,5 mg·kg⁻¹ iv afin d'obtenir des conditions excellentes pour l'insertion d'un masque laryngé (LMA®) chez 95 % de patientes adultes.

Méthode Soixante-huit patientes adultes ASA I et II prémédiquées et nécessitant une anesthésie pour une chirurgie ambulatoire ont été randomisées en quatre groupes selon la dose de rémifentanyl (0,25, 0,5, 1 ou 2 µg·kg⁻¹). L'induction de l'anesthésie a été réalisée avec l'une des quatre doses de rémifentanyl en aveugle perfusée sur 60 secondes, administrée simultanément à du propofol 2,5 mg·kg⁻¹ iv perfusé sur 45 secondes. L'insertion du

LMA a été essayée 150 sec après le début de la séquence d'induction. Les conditions d'insertion ont été évaluées à l'aide d'une note en six catégories selon la résistance à l'ouverture de la bouche et à l'insertion, la déglutition, la toux et le réflexe pharyngé, le mouvement et le laryngospasme. Une analyse par la méthode des probits a été réalisée de façon à calculer la dose efficace nécessaire à une insertion du LMA chez 95 % des patientes [dose efficace (DE)₉₅]. Les changements de fréquence cardiaque et de tension artérielle moyenne en réaction à l'insertion du LMA ont été enregistrés et comparés comme variables secondaires.

Résultats La DE₉₅ de rémifentanyl était de 1,32 [intervalle de confiance (IC) 95 % : 0,99-2,46] $\mu\text{g}\cdot\text{kg}^{-1}$. Les changements au niveau de la fréquence cardiaque et de la tension artérielle moyenne étaient modestes et semblables au fil du temps dans les groupes, avec des diminutions maximales de la fréquence cardiaque et de la tension artérielle moyenne < 30 % chacune pendant l'induction de l'anesthésie.

Conclusion La dose de rémifentanyl nécessaire pour obtenir des conditions excellentes pour l'insertion du LMA chez 95 % des patientes lorsqu'il est administré conjointement à du propofol 2,5 $\text{mg}\cdot\text{kg}^{-1}$ chez des patientes saines prémédiquées et subissant une chirurgie ambulatoire non urgente est de 1,32 (IC 95 % : 0,99-2,46) $\mu\text{g}\cdot\text{kg}^{-1}$.

Successful insertion of the laryngeal mask airway (LMATM) requires adequate mouth opening and sufficient depth of anesthesia to prevent untoward events of coughing, gagging, movements, and laryngospasm. It has been shown that propofol 2.5-3.5 $\text{mg}\cdot\text{kg}^{-1}$, rather than thiopental 4-5 $\text{mg}\cdot\text{kg}^{-1}$,¹⁻³ combined with alfentanil, rather than fentanyl⁴, provides superior conditions for the insertion of the LMA. Thus, the optimal alfentanil dosage providing excellent insertion conditions in 95% of patients when co-administered with 2.5 $\text{mg}\cdot\text{kg}^{-1}$ propofol was previously assessed.⁵

Remifentanyl is an ultra-short-acting selective μ -opioid receptor agonist that is 20-30 times more potent than alfentanil. Due to its pharmacokinetic properties, the use of remifentanyl is of particular interest whenever maintenance of sufficient analgesia level is required during the procedure.⁶ Its combination with propofol significantly improved the ease of insertion of the LMA in comparison with propofol alone.^{7,8} The optimum effect-site concentration (EC) of remifentanyl for LMA insertion during target-controlled infusion of propofol was recently determined through use of a modified Dixon's up-and-down method followed by a probit analysis for the EC₉₅ estimation.⁹ However, the effective dose of remifentanyl providing excellent insertion conditions in 95% of patients

(efficient dose [ED]₉₅) when co-administered with a single standard dose of propofol has not been assessed.

Therefore, using an optimized sequence for induction of anesthesia, we conducted a dose-response study to determine the effective dose of remifentanyl co-administered with propofol 2.5 $\text{mg}\cdot\text{kg}^{-1}$ that would provide excellent insertion conditions in 95% of patients (ED₉₅) undergoing ambulatory elective surgery.¹⁰ The secondary outcome variables included calculation of the ED₅₀, qualitative analysis of the criteria used for the assessment of the insertion conditions of the LMA according to the remifentanyl dosages, and hemodynamic tolerance (heart rate [HR] and mean arterial pressure [MAP]).

Methods

The study took place in our department of anesthesia for gynecological surgery at the Édouard Herriot Hospital, Lyon, France. After Hospital Ethics Committee approval of the study and after obtaining the patients' written consent, we enrolled caucasian female patients who were scheduled for elective outpatient gynecological surgery requiring the use of LMA. Inclusion criteria included patients aged 18 to 70 yr who were American Society of Anesthesiologists (ASA) physical status I and II and had a body mass index < 30 $\text{kg}\cdot\text{m}^{-2}$. Exclusion criteria included patients with a history or evidence of a difficult airway (combination of the Mallampati score 3 or 4, thyromental distance < 60 mm,^{11,12} and mouth opening of < 35 mm) and patients with risk factors for pulmonary aspiration of gastric contents.

Anesthetic protocol

All patients were premedicated with alprazolam 0.5 mg and hydroxyzine 1 $\text{mg}\cdot\text{kg}^{-1}$ orally given one hour before induction of anesthesia.

Patients were randomly allocated by a computer-generated list in a single sequence of random assignment with no restriction (simple randomization) to receive one of four doses of remifentanyl (0.25, 0.5, 1, or 2 $\mu\text{g}\cdot\text{kg}^{-1}$). The range of doses of remifentanyl for the insertion of the LMA was selected based on the following assumptions: the required dose of remifentanyl would be less than twice the dose required to moderate hemodynamic responses to tracheal intubation and more than one-fourth of a 4 $\mu\text{g}\cdot\text{kg}^{-1}$ dose determined from a recent study in a similar population,¹³ and as was previously reported when using alfentanil in combination with propofol.⁵ The randomization list was generated by a physician who was not involved in the enrollment of patients into the study. Allocation concealment was ensured by the use of coded

sealed opaque envelopes. Remifentanyl was diluted with 0.9% saline 50 $\mu\text{g}\cdot\text{mL}^{-1}$ into a 50 mL syringe.

Following application of routine monitors in the operating room, the patients were pre-oxygenated until their end-tidal oxygen fractions were $> 90\%$, then anesthesia was induced. At time T_0 , the chosen dose of remifentanyl was infused over 60 sec using a programmable syringe pump, Pilote Anesthésie 2®, (Fresenius Vial, Brezins, France) hidden behind a sheet, followed by a continuous infusion of 0.15 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Propofol 2.5 $\text{mg}\cdot\text{kg}^{-1}$ was simultaneously administered over 45 sec. Ventilation via facemask was initiated once loss of eyelash reflex occurred.

The same experienced senior physician who was blinded to the anesthetic procedure performed all LMA (AuraOnce™, Ambu®, Ballerup, Denmark) insertions. A size 3 LMA was selected for patients < 65 kg, and a size 4 LMA was used for all other patients. At time $T_0 + 150$ sec, the physician attempted to insert the LMA according to the technique recommended by Brain *et al.*,¹⁴ and assessed the quality of insertion as described further. If insertion conditions were judged to be uncomfortable, supplemental boluses of remifentanyl 1 $\mu\text{g}\cdot\text{kg}^{-1}$ and/or propofol 0.5 $\text{mg}\cdot\text{kg}^{-1}$ were administered at the discretion of the inserting anesthesiologist.

Anesthesia was maintained with 1.5–2% end-tidal sevoflurane in 50% oxygen, and continuous infusion of remifentanyl 0.15 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. The lungs were ventilated to normocapnia. No further stimulation was applied to the patient during the study period.

Monitors included an automated arterial pressure cuff, electrocardiogram, peripheral pulse oximeter, and capnometer. Control values of arterial pressure and HR were recorded before induction of anesthesia (pre-induction values), one, three, five, and ten minutes after the end of propofol infusion. If MAP or HR decreased more than 30% compared with corresponding pre-induction values, ephedrine 3 mg or atropine 0.5 mg was administered intravenously, as needed to reach at least 70% of the pre-induction value.

Assessment of the LMA insertion conditions

Insertion conditions were assessed with a scale used successfully in previous studies.^{4,5} Six variables were recorded: resistance to mouth opening, resistance to insertion of LMA, swallowing, coughing and gagging, head or body movement, and laryngospasm, as defined by prolonged obstruction with an apparently correctly placed LMA. Each of these variables was rated as excellent or intermediate or poor. The criteria for assigning values to each variable are set out in Table 1. The LMA insertion conditions were excellent if all criteria were scored as excellent, intermediate if all criteria were scored as either

Table 1 Scoring conditions for LMA insertion

Variable	Insertion conditions		
	Excellent	Intermediate	Poor
Mouth opening	No	Significant	Undue force required
Ease of LMA insertion	No	Significant	Undue force required
Patient response			
Swallowing	Nil	Slight	Gross
Coughing and gagging	Nil	Slight	Gross
Head and body movements	Nil	Slight	Gross
Laryngospasm	Nil	Partial	Total

LMA insertion conditions: excellent, all responses are excellent; intermediate, all responses are excellent or intermediate; poor, the presence of one or more poor responses. LMA = laryngeal mask airway

excellent or intermediate, and poor if a single criterion was scored as poor. The number of LMA insertion attempts was also recorded for each patient.

Statistical analysis

In a Cochran-Armitage test for trend in proportions, a sample size of 17 patients per group was obtained from four groups with remifentanyl doses equivalent to 0.25, 0.5, 1, and 2 $\mu\text{g}\cdot\text{kg}^{-1}$ and proportions of excellent LMA insertion conditions equivalent to 0.40, 0.60, 0.80, and 0.90 $\mu\text{g}\cdot\text{kg}^{-1}$, respectively. A sample size of 68 subjects achieves 90% power to detect a linear trend using a two-sided Z test with continuity correction and a significance level of 0.05 (PASS 8.0.05 [NCSS, LCC, Kaysville, UT, USA]).¹⁵

The computer software package, Statistica 6.0 (Statsoft®, Tulsa, OK, USA), was used for analysis of the hemodynamic data. Median doses of ephedrine were analyzed using the Kruskal-Wallis H test. Repeated measures of hemodynamic values were analyzed by a two-way analysis of variance. The χ^2 test was used to analyze the incidence of requiring supplemental bolus doses of remifentanyl and propofol, the incidence of requiring ephedrine, the overall LMA insertion conditions in the four patient groups distributed according to remifentanyl dosages, and the quality of the six criteria used to assess the LMA insertion conditions. For each outcome measured, whenever the result of the χ^2 test reported a significant difference between groups ($P < 0.05$), a Bonferroni adjustment for multiple comparisons was made over the six between-dose comparisons, with a cut-off of $0.05/6 = 0.0083$, which was considered to be statistically significant.

The event “success” or “failure” of excellent insertion conditions for each patient was analyzed using Statistical Package for Social Science version 16.0 (SPSS®, Chicago,

IL, USA) for probit regression to calculate the effective dose of remifentanyl required to provide excellent insertion conditions in 50% and 95% of patients (ED_{50} and ED_{95}). Probit analysis is designed to model the probability of response to a stimulus in the setting of a dose-response experiment. Since the probability of an event must lie from 0 to 1, it is impractical to model probabilities with linear regression techniques, because the linear regression model allows the dependent variable to take values greater than 1 or less than 0. The probit analysis model is a type of generalized linear model that extends the linear regression model by linking the range of real numbers to the 0-1 range in a sigmoid relationship. Sigmoid relationships can be linearized by transformations such as logit and probit. The fitted model is assessed by statistics for heterogeneity which follow a Chi square distribution. If the heterogeneity statistics are significant, then the observed values deviate from the fitted curve too much for reliable inference to be made. Probit regression gives the effective levels of dose/stimulus with confidence intervals (CI) at the specified quantiles, e.g., ED_{50} or ED_{95} , with the curve fitted by maximum likelihood estimation.

Results

Eighty-seven patients were screened for this study. Four were excluded because they refused to participate, and 15 did not meet the inclusion criteria. Sixty-eight patients were enrolled (17 patients per group) from May to December 2008. All included patients completed the study. Patients' characteristics are shown in Table 2. All subjects were female.

The overall and individual insertion scores are summarized in Figures 1 and 2. For eight patients (five from group 0.25 $\mu\text{g}\cdot\text{kg}^{-1}$ and three from group 0.5 $\mu\text{g}\cdot\text{kg}^{-1}$), insertion conditions were judged poor. Laryngeal mask airway insertion was achievable in all of the patients; however, six patients required more than one attempt at LMA placement. With Bonferroni adjustments for multiple comparisons, overall insertion conditions in group 0.25 $\mu\text{g}\cdot\text{kg}^{-1}$ were considerably different from group 2 $\mu\text{g}\cdot\text{kg}^{-1}$ (Figure 1). There was no significant difference between groups regarding coughing and gagging, head or body movements, and

Fig. 1 Overall insertion conditions of the laryngeal mask airway (LMA) in the four groups of remifentanyl dosages. $P = 0.0023$ between groups. * $P = 0.0003$ compared with group 2 $\mu\text{g}\cdot\text{kg}^{-1}$ regarding overall insertion conditions, and † $P = 0.0002$ compared with group 2 $\mu\text{g}\cdot\text{kg}^{-1}$ regarding excellent vs non-excellent conditions (Bonferroni adjustments for multiple comparisons)

laryngospasm (Figure 2). Concerning resistance to mouth opening and resistance to inserting the LMA (Figures 2a and d), there were statistically significant differences between group 0.25 $\mu\text{g}\cdot\text{kg}^{-1}$ and group 2 $\mu\text{g}\cdot\text{kg}^{-1}$, with group 0.25 $\mu\text{g}\cdot\text{kg}^{-1}$ having less excellent conditions. Nevertheless, there was no statistically significant difference between groups regarding the rate of undue force required. After Bonferroni adjustments for multiple comparisons, we were unable to locate the difference reported between groups regarding the rate of swallowing (Figure 2b).

No difference was recorded between groups with respect to the requirement for supplemental administration of remifentanyl and propofol (Table 3). From probit analysis, the ED_{50} of remifentanyl was 0.44 $\mu\text{g}\cdot\text{kg}^{-1}$ (95% CI 0.11–0.64 $\mu\text{g}\cdot\text{kg}^{-1}$) and the ED_{95} was 1.32 $\mu\text{g}\cdot\text{kg}^{-1}$ (95% CI 0.99–2.46 $\mu\text{g}\cdot\text{kg}^{-1}$) (omnibus test of model coefficients: $\text{Chi} = 24.28$; $\text{df} = 1$; $P < 0.01$) (Figure 3).

For all four groups of patients, two-way analysis of variance of HR and MAP showed a significant decrease in HR and MAP following induction, without any significant

Table 2 Patient characteristics

Remifentanyl dose ($\mu\text{g}\cdot\text{kg}^{-1}$)	0.25 ($n = 17$)	0.5 ($n = 17$)	1 ($n = 17$)	2 ($n = 17$)
Age (yr)	46 (29–59)	35 (29–41)	32 (27–57)	43 (27–53)
Body mass index ($\text{kg}\cdot\text{m}^{-2}$)	23 (22–25)	22 (21–24)	24 (21–28)	22 (20–25)
ASA class I/II (n)	13/4	13/4	11/6	13/4
Mallampati class 1/2 (n)	10/7	13/4	9/8	12/5

Data are median (interquartile range), or number of patients (n)

Fig. 2 Distribution of patients in the four groups of remifentanyl dosages based on the quality of the six criteria used for assessing laryngeal mask airway (LMA) insertion conditions. **a** * $P = 0.022$ between groups. $^{\dagger} P = 0.008$ compared with group $2 \mu\text{g}\cdot\text{kg}^{-1}$ regarding resistance to mouth opening, and $^{\ddagger} P = 0.003$ compared with group $2 \mu\text{g}\cdot\text{kg}^{-1}$ regarding excellent vs non excellent conditions (Bonferroni adjustments for multiple comparisons). **b** ** $P = 0.0046$ between groups. **d** $^{\S} P = 0.018$ between groups. $^{\parallel} P = 0.0053$ compared with group $2 \mu\text{g}\cdot\text{kg}^{-1}$ regarding resistance to insertion, and $^{\#} P = 0.0012$ compared with group $2 \mu\text{g}\cdot\text{kg}^{-1}$ regarding excellent vs non excellent conditions (Bonferroni adjustments for multiple comparisons)

Table 3 Anesthetic characteristics

Remifentanyl dose ($\mu\text{g}\cdot\text{kg}^{-1}$)	0.25 ($n = 17$)	0.5 ($n = 17$)	1 ($n = 17$)	2 ($n = 17$)
Supplemental bolus of remifentanyl (n)	5	2	2	0
Supplemental bolus of propofol (n)	2	2	1	0
Ephedrine requirement (n)	4	1	3	5
Total dose of administered ephedrine for each patient (mg)	3, 6, 6, 9	6	6, 6, 6	6, 6, 6, 9, 9

Data are either number of patients (n) or mg for each patient having received ephedrine

difference between groups (Figure 4). The greatest decrease in mean values of HR and MAP was recorded five minutes after propofol administration, and the range across the four groups was 19–22% for HR and 27–29% for MAP (Figure 4). No statistical difference was found between groups with respect to ephedrine requirements (Table 3). No patient required atropine.

Discussion

This dose-response study allowed us to determine the ED_{95} of remifentanyl co-administered with propofol $2.5 \text{ mg}\cdot\text{kg}^{-1}$ in elective adult female patients.

Several previous studies demonstrated that adding an opioid to propofol significantly improved LMA insertion

Fig. 3 Probit regression of the probability of excellent laryngeal mask airway (LMA) insertion conditions as a function of the induction dose of remifentanyl. Horizontal bars denote 95% confidence interval for inserting efficient dose (ED) in 50% and 95% of patients (ED₅₀ and ED₉₅). Omnibus test of model coefficients: Chi = 24.28; df = 1; $P < 0.01$

conditions. Thus, when co-administered with propofol, alfentanil was reported to be superior to fentanyl for reaching excellent insertion conditions,⁴ and the optimal dose of alfentanil was $10 \mu\text{g}\cdot\text{kg}^{-1}$ when co-administered with propofol $2.5 \text{ mg}\cdot\text{kg}^{-1}$.⁵ However, compared with remifentanyl, the context-sensitive half-times of alfentanil do not always allow prolonged infusion or repeated administration of this opioid due to the potential for alfentanil drug cumulation over time.^{6,16} Remifentanyl is an ultra-short-acting opioid with a context-sensitive half-time that is independent of the duration of drug administration.⁶ Therefore, remifentanyl has a pharmacokinetic profile well-suited for rapid recovery, even for more prolonged outpatient procedures requiring moderate or high levels of intraoperative analgesia. Its addition to propofol, remifentanyl significantly improved LMA insertion conditions during induction of anesthesia.^{7,8} In a recent study, Kim *et al.*⁹ reported that $3.79 \text{ ng}\cdot\text{mL}^{-1}$ is the optimum effect-site concentration of remifentanyl for LMA insertion during target-controlled infusion of propofol $3.5 \mu\text{g}\cdot\text{mL}^{-1}$. However, it remains difficult to compare these results with ours, since the model of administration of propofol and remifentanyl was considerably different, and the modified Dixon's up-and-down method followed by probit analysis methodology used in Kim *et al.*'s study for estimating the EC₉₅ value¹⁰ resulted in a very large 95% CI for the EC₉₅ (from 3.26 to $9.25 \text{ ng}\cdot\text{mL}^{-1}$).⁹

As expected, we observed a decrease in the ED₉₅ of remifentanyl for providing excellent LMA insertion conditions compared with the IED₉₅ of remifentanyl $4 \mu\text{g}\cdot\text{kg}^{-1}$.¹³ This decrease was due to use of a carefully standardized anesthetic induction sequence and consideration of the

Fig. 4 Mean hemodynamic changes in the four groups of the study. Error bars represent 95% confidence intervals. * $P < 0.001$ vs baseline values. No significant statistical difference between groups

unique pharmacokinetic and pharmacodynamic attributes of propofol and remifentanyl such that LMA insertion occurred at the time when effect-site concentration peaked for both agents.^{17,18} In fact, insertion of the LMA constitutes a less noxious stimulus compared with laryngoscopy. Billard *et al.* observed a significant increase in systolic blood pressure ($> 40\%$) during laryngoscopy and tracheal intubation after induction of anesthesia with propofol $2.5 \text{ mg}\cdot\text{kg}^{-1}$ given alone,¹⁹ whereas Hickey *et al.*²⁰ reported minor cardiovascular response to insertion of LMA after the same dose of propofol. Yu *et al.*⁵ calculated that the optimum dose of alfentanil for inserting the classic LMA was $10 \mu\text{g}\cdot\text{kg}^{-1}$ when co-administered with propofol $2.5 \text{ mg}\cdot\text{kg}^{-1}$, which corresponds to one-fourth of the required dose of alfentanil for tracheal intubation when co-administered with propofol $2 \text{ mg}\cdot\text{kg}^{-1}$.²¹ Therefore, it is not surprising that ED₉₅ of

remifentanyl for LMA insertion is lower than the dose required for tracheal intubation.

Increasing doses of remifentanyl significantly improved LMA insertion conditions, mainly by decreasing resistance to both mouth opening and insertion. In the study by Yu *et al.*⁵ in which they assessed the ED₉₅ of alfentanil combined with propofol for LMA insertion, the addition of alfentanil did not provide reliable mouth opening or a reduction in resistance to insertion. For these authors, these two assessments may have been influenced by anatomical variations of the upper airway, which are different in ethnic Chinese compared with the Caucasian population for whom the anatomic characteristics of the LMA were originally designed.⁴ Only Caucasian patients were included in our study to minimize the impact of this feature as a potentially confounding variable. Mouth opening and resistance to insertion are essential criteria that must be optimized for ease of LMA insertion.

No clinically significant muscle rigidity was observed in either group. Muscle rigidity was described after rapid infusion of large doses of opioids;²² therefore, in our study, remifentanyl was administered over 60 sec. Similarly, no muscular rigidity was observed in previous studies with doses of remifentanyl ranging from 1 to 4 $\mu\text{g}\cdot\text{kg}^{-1}$ administered over 90 sec in combination with propofol 2 $\text{mg}\cdot\text{kg}^{-1}$ or thiopental 5 $\text{mg}\cdot\text{kg}^{-1}$ for tracheal intubation.^{23,24} Moreover, alprazolam given 60 min prior to induction of anesthesia may also have contributed to minimizing the occurrence of muscle rigidity, since pre-medication with benzodiazepine is effective in preventing opioid-induced muscle rigidity.²⁵

Hemodynamic tolerance was similar and acceptable in the four groups of our study. The maximum decrease in mean values of HR and MAP was less than 30%, and there was no significant increase in the requirement of ephedrine administration across the four groups. Several previous studies reported a similar acceptable decrease in the MAP and HR when using varying amounts of remifentanyl (from 0.5 to 5 $\mu\text{g}\cdot\text{kg}^{-1}$) combined with propofol 2.0 or 2.5 $\text{mg}\cdot\text{kg}^{-1}$.^{23,26} In fact, in ASA I and II patients, it has been reported that co-administration of fentanyl (2 or 4 $\mu\text{g}\cdot\text{kg}^{-1}$) with increased doses of propofol (from 2 to 3.5 $\mu\text{g}\cdot\text{kg}^{-1}$) did not exacerbate a decrease of either blood pressure or HR while it attenuated the cardiovascular response to laryngoscopy in comparison with placebo.¹⁹ In the same way, the addition of remifentanyl 0.25 or 0.5 $\mu\text{g}\cdot\text{kg}^{-1}$ to propofol 2.5 $\text{mg}\cdot\text{kg}^{-1}$ was well tolerated and moderated cardiovascular responsiveness to LMA insertion that were present when no opioid was co-administered with propofol.^{7,19,20}

There are several limitations of our study. First, only female patients were included, as this study was conducted in a gynecological unit. Although a gender effect in opioid

analgesic responsiveness remains controversial, it would be of interest to perform a similar dose response study in male patients.^{27,28} Second, our results are available for ASA I and II patients only, aged 18 to 70 yr. Hemodynamic tolerance in ASA III or IV patients may be different, particularly those suffering from serious heart disease. A further limitation of the study is that the sample size calculation was not based on the primary objective of the study, i.e., the estimation of ED₉₅, limiting the precision of the ED₉₅ estimate. Therefore, it would be of interest to perform a larger study focusing on a smaller dose range to more precisely determine the ED₉₅.

In conclusion, our study investigated the optimal dose of remifentanyl combined with propofol 2.5 $\text{mg}\cdot\text{kg}^{-1}$ to provide excellent LMA insertion conditions in 95% of healthy patients. Although the estimate of the ED₉₅ value is not sufficiently precise to draw firm conclusions, we suggest using remifentanyl 1.20 to 1.40 $\mu\text{g}\cdot\text{kg}^{-1}$ *iv* given over 60 sec and started 150 sec before insertion of the LMA when using propofol in healthy adult patients.

Competing interests None declared.

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