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ORIGINAL ARTICLE

# The effective bolus dose of remifentanil to facilitate laryngeal mask airway insertion during inhalation induction of sevoflurane in children

**Hyuckgoo Kim[1] · Sung Mee Jung[1] · Sang-Jin Park[1]**

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**Abstract**
*Purpose* The additional administration of remifentanil during inhalation induction with sevoflurane could provide better conditions for laryngeal mask airway (LMA) insertion than sevoflurane alone. This study was designed to evaluate the 50 % effective bolus dose ($ED_{50}$) and 95 % effective bolus dose ($ED_{95}$) of remifentanil required for LMA insertion in children during inhalation induction with sevoflurane.
*Methods* Pediatric patients aged 3–12 years requiring general anesthesia were recruited. A predetermined dose of remifentanil was injected over 30 s after the induction of general anesthesia with sevoflurane. LMA insertion was attempted 60 s after remifentanil injection. The dose of remifentanil was determined using the Dixon's up-and-down method, starting from 0.5 μg/kg (step size of 0.05 μg/kg).
*Results* The study was conducted until seven cross-over points and 29 children were collected. The $ED_{50}$ of remifentanil for successful LMA insertion during sevoflurane inhalation induction in children was 0.168 ± 0.035 μg/kg using Dixon's method. In addition, the $ED_{50}$ and $ED_{95}$ of remifentanil from the probit analysis were 0.176 μg/kg (95 % confidence limits, 0.102–0.216 μg/kg) and 0.268 μg/kg (95 % confidence limits, 0.223–0.659 μg/kg), respectively.
*Conclusion* The $ED_{50}$ and $ED_{95}$ of remifentanil for successful LMA insertion in children were estimated to be 0.176 (0.168) and 0.268 μg/kg during inhalation induction with 2.1 % sevoflurane.

✉ Sang-Jin Park
apsj0718@naver.com

[1] Department of Anesthesiology and Pain Medicine, College of medicine, Yeungnam University, Daegu 705-703, Republic of Korea

**Keywords** Laryngeal mask airway · Remifentanil · Sevoflurane

## Introduction

Inhalation induction with sevoflurane is commonly used to facilitate insertion of a laryngeal mask airway (LMA) in children. However, some studies have reported that complications including coughing and body movement, or bradycardia and hypotension requiring treatment were observed despite the use of sevoflurane at a concentration of ≥4 % [1, 2]. Therefore, sevoflurane alone may not prevent undesirable responses during LMA insertion and high concentrations of sevoflurane may induce hemodynamic instability.

The additional administration of opioids during inhalation induction with sevoflurane provides better conditions for LMA insertion than sevoflurane alone [3]. Remifentanil, a potent, ultra-short-acting opioid, is considered to be effective in preventing the response to short-term noxious stimulations such as LMA insertion. However, the optimal bolus dose of remifentanil for LMA insertion during inhalation induction with sevoflurane in pediatric anesthesia has not been established. The current study, therefore, was designed to evaluate the 50 % effective bolus dose ($ED_{50}$) and 95 % effective bolus dose ($ED_{95}$) of remifentanil required for LMA insertion in children during sevoflurane induction using the Dixon's up-and-down method.

## Methods

The study was approved by the Institutional Review Board of the authors' institute and was registered in a clinical

trial registry before recruitment of the first subject (ClinicalTrials.gov, ID: NCT01919203). Children undergoing elective strabismus surgery (bilateral lateral rectus muscle recession, unilateral lateral rectus muscle recession and medial rectus muscle resection) under general anesthesia were enrolled. The children who were aged between 3 and 12 years of age were American Society of Anesthesiologists Physical Status I. Written informed consent for the study was obtained from the parents of all children. Patients with an abnormal airway, history of upper respiratory infection within 3 weeks, reactive airway disease, gastroesophageal reflux, psychological or developmental disorder, or history of allergy to the drugs used in our protocol were excluded. We also excluded children whose parents refused to consent.

Patients received intravenous administration of midazolam 0.05 mg/kg to reduce separation anxiety before arrival in the operating room. Upon arrival in the operating room, electrocardiography, pulse oximetry ($SpO_2$), end-tidal $CO_2$ ($EtCO_2$), noninvasive arterial blood pressure, bispectral index (BIS), and inhaled and exhaled end-tidal sevoflurane concentration (ETsevo) were monitored in all patients. The lungs were ventilated with 8 % sevoflurane in 100 % $O_2$ at a flow rate of 6 L/min for anesthetic induction. After loss of consciousness, atropine 0.01 mg/kg was administered intravenously to prevent unwanted autonomic vagal reflex associated with anesthetic induction and strabismus surgery [4]. A vaporizer was controlled in order to maintain 2.1 % ETsevo. We selected this dose of sevoflurane because the minimum alveolar concentration (MAC) is approximately 2.16 % at 10 years of age [5]. After anesthesia was maintained with 2.1 % ETsevo for 10 min, the predetermined dose of remifentanil was injected over 30 s. Insertion of LMA was attempted 60 s after administration of remifentanil. The size of the LMA was determined according to the manufacturer's guidelines, which recommend size 2 for individuals weighing 6.5–20 kg, size 2.5 for 20–30 kg, and size 3 for 30–50 kg.

The target dose of remifentanil for an individual patient was determined according to the response of a previous patient, using the Dixon's up-and-down sequential method [6]. The dose of remifentanil started at 0.5 μg/kg. This dose of remifentanil was selected because a previous study reported that the $ED_{50}$ of remifentanil for successful LMA insertion during induction with 2.5 mg/kg propofol was 0.56 μg/kg in children [7]. If the LMA was inserted successfully into the patient, the predetermined dose of remifentanil for the subsequent patient was decreased by 0.05 μg/kg. Similarly, if LMA insertion failed, the predetermined remifentanil dose was increased by 0.05 μg/kg for the next patient. When LMA insertion failed, a muscle relaxant (rocuronium 0.5 mg/kg) was administered intravenously and the lungs were ventilated with a mask. Insertion of the LMA was attempted again 3 min later. If this attempt also failed, tracheal intubation was performed for surgery. The primary endpoint of this study was the response to LMA insertion. This composite response included development of gross purposeful movement, coughing, gagging, inadequate jaw relaxation (clenching), and upper airway obstruction such as laryngospasm. The response of the patient was observed until 2 min after LMA insertion and evaluated as failure or success. Failure of LMA insertion was defined as any of the above-mentioned responses. Success of LMA insertion was defined as the absence of the above responses.

When the LMA was inserted, the predetermined dose of remifentanil and the result (failure or success) were recorded. Systolic and diastolic blood pressure (SBP, DBP), heart rate (HR), $SpO_2$, and BIS were recorded at the following time-points—arrival in the operating room, when ETsevo reached 2.1 %, just before remifentanil administration, just before LMA insertion, 1 min after LMA insertion, and 4 min after LMA insertion. In addition, the duration of anesthesia and surgery and the LMA insertion time (from the time of passing the LMA between the teeth to the time of the appearance of $EtCO_2$) were recorded. Significant bradycardia (HR < 65 beats/min at 3–6 years of age, <60 beats/min at 7–12 years of age) [8] and hypotension (over 30 % decrease from baseline SBP) [9] were also recorded. Two anesthetists participated in the insertion of the LMA. The first practitioner knew the predetermined dose of remifentanil for each patient, whereas the second practitioner did not. The first anesthetist performed the remifentanil injection and recorded the following variables—vital signs, BIS, ETsevo, LMA insertion time, and the duration of anesthesia and surgery. The second anesthetist, who was blinded to the dose of remifentanil, performed the LMA insertion and recorded the result as a success or failure.

Data were presented as number or mean ± SD. The number of patients was based on the Dixon's up-and-down method. This method requires at least six cross-over points (successful insertion to failed insertion) for statistical analysis [6, 10]. The current study was conducted until data of seven cross-over points were collected. The $ED_{50}$ was defined as the average of the midpoint doses in each pair. The up-and-down sequences were analyzed using the probit test, which derives the dose of remifentanil for LMA insertion with 95 % confidence limits of the mean. We made maximal likelihood estimates of the model variables and a goodness-of-fit estimate using a probit analysis that presented the best-fitting sigmoid curve. Comparison of BIS before LMA insertion between successful insertion and failed insertion was performed using the *t* test after a normality test. Changes of SBP, DBP, and HR during induction were analyzed using repeated measures ANOVA

with Bonferroni's post hoc testing. Statistical analysis was performed using SPSS 21.0 (IBM, Armonk, NY, USA). A $P$ value <0.05 was considered statistically significant.

## Results

The study included patients until seven cross-over points were achieved. Of thirty-nine consecutive children eligible for this study, 8 were excluded for refusal to give consent ($n = 5$) and upper respiratory infection within 3 weeks ($n = 3$). Of the 31 enrolled patients, 2 children were excluded before anesthesia induction due to BIS monitor malfunction. Twenty-nine children completed the study. Demographic data and induction profiles are shown in Table 1. BIS before LMA insertion did not differ significantly between patients with successful insertion and patients with unsuccessful insertion (Table 2). The causes of failure are shown in Table 2. The sequences of successful insertion and unsuccessful insertion are illustrated in Fig. 1. The required dose of remifentanil for successful LMA insertion was 0.168 ± 0.035 μg/kg using Dixon's method. A dose–response curve from the probit analysis of the remifentanil dose and the probability of successful insertion of LMA is shown in Fig. 2. This showed that the $ED_{50}$ and $ED_{95}$ of remifentanil for successful insertion of LMA were 0.176 μg/kg (95 % confidence limits 0.102–0.216 μg/kg) and 0.268 μg/kg (95 % confidence limits 0.223–0.659 μg/kg), respectively. Maximum likelihood estimation revealed $P = 0.985$ and chi-squared goodness-of-fit $\chi^2 = 1.428$.

Hemodynamic data from all participants are shown in Table 3. Blood pressures before and after LMA insertion were significantly lower than the baseline value ($P < 0.05$). HR during anesthesia induction was higher compared with the baseline value ($P < 0.05$). However, there were no patients with significant hypotension or bradycardia. Laryngospasm secondary to airway obstruction also did not occur.

**Table 1** Demographic data and induction profiles

| | |
|---|---|
| Sex (M/F) | 13/16 |
| Age (years) | 7.3 ± 1.6 |
| Weight (kg) | 28.4 ± 8.1 |
| Height (cm) | 125.6 ± 10.0 |
| BIS just before LMA insertion | 53.9 ± 5.6 |

Data are expressed as number or mean ± SD

*BIS* bispectral index, *LMA* laryngeal mask airway

**Table 2** Comparison of induction profiles between success and failure in LMA insertion

| | Success group | Fail group | $P$ value |
|---|---|---|---|
| Number | 18 | 11 | |
| BIS just before LMA insertion | 54.7 ± 5.4 | 52.2 ± 5.8 | 0.254 |
| Insertion time of LMA | 24.1 ± 9.2 | | |
| Cause of failure | | | |
| Movement | 0 | 7 | |
| Poor relaxation of jaw | 0 | 3 | |
| Cough | 0 | 1 | |

Data are expressed as number or mean ± SD

Success group: successful LMA insertion, fail group: unsuccessful LMA insertion

*LMA* laryngeal mask airway

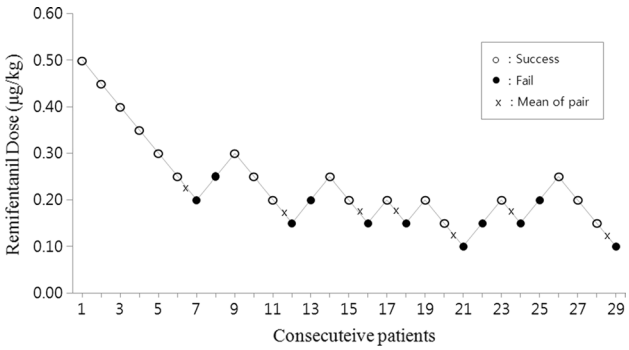


**Fig. 1** The dose of remifentanil in 29 consecutive patients in whom laryngeal mask airway (LMA) was inserted. The response of each patient is represented with a *blanked* or *black circle*. *Cross* indicates the midpoint dose of an independent pair of patients involving success to failure of LMA insertion. The dose of remifentanil at which a successful LMA insertion is possible in 50 % of children was 0.168 ± 0.035 μg/kg

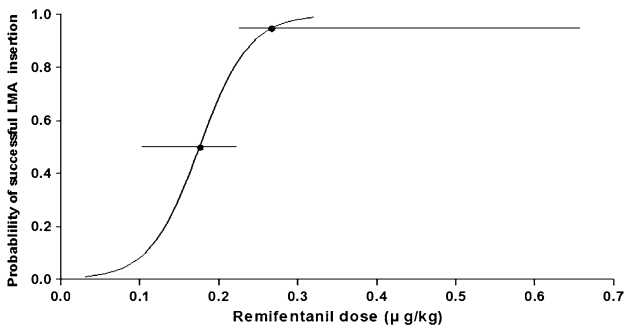


**Fig. 2** Dose–response curve for remifentanil plotted from the probit analyses of individual dose and the respective patient responses to insertion of laryngeal mask airway (LMA). The doses of remifentanil at which there were 50 and 95 % probabilities of successful LMA insertion were 0.176 μg/kg (95 % confidence limits 0.102–0.216 μg/kg) and 0.268 μg/kg (95 % confidence limits 0.223–0.659 μg/kg), respectively. *Open circles* represent the 50 and 95 % probability points fitting a dose–response curve from the probit analysis and the *horizontal bars* represent the 95 % confidence limits for these points

**Table 3** Blood pressure and heart rate during anesthesia induction

| | Arrival in operating room | Attainment of ETsevo 2.1 % | Just before remifentanil injection | Just before LMA insertion | 1 min after LMA insertion | 4 min after LMA insertion |
|---|---|---|---|---|---|---|
| SBP | 112.2 ± 11.7 | 109.0 ± 13.5 | 101.0 ± 10.3* | 100.0 ± 9.0* | 106.5 ± 14.6 | 103.4 ± 9.3* |
| DBP | 65.4 ± 8.4 | 60.0 ± 11.1 | 53.0 ± 8.2* | 52.1 ± 7.4* | 58.4 ± 12.3 | 54.5 ± 7.5* |
| HR | 87.6 ± 13.6 | 95.1 ± 17.6 | 101.6 ± 17.8* | 106.7 ± 15.9* | 112.6 ± 17.9* | 114.1 ± 14.1* |

Data are expressed as mean ± SD

*ETsevo* end-tidal sevoflurane concentration, *SBP* (mmHg) systolic blood pressure, *DBP* (mmHg) diastolic blood pressure, *HR* (beats/min) heart rate

* $P < 0.05$ compared with arrival in operating room

## Discussion

In the present study, we evaluated the effective bolus dose of remifentanil for LMA insertion when anesthesia is induced with sevoflurane in children. We found that the $ED_{50}$ and $ED_{95}$ of remifentanil for successful LMA insertion were 0.176 and 0.268 μg/kg, respectively, when injected as a bolus over 30 s. During anesthesia induction from inhalation of sevoflurane after LMA insertion, none of the children suffered from any serious complications such as laryngospasm, or hypotension and bradycardia requiring treatment.

A previous study reported that the $ED_{50}$ and $ED_{95}$ of sevoflurane for the achievement of successful LMA insertion were 1.57 and 2.22 % end-tidal concentration, respectively, in pediatric patients [11]. However, we found that administration of additional remifentanil was required for successful LMA insertion, even if ETsevo was maintained at 2.1 % during induction. In addition, it has been reported that the value of sevoflurane for a 50 % probability of successful LMA insertion was 2.0 % in children [12]. Research on the concentration of sevoflurane required for LMA removal has reported that the $ED_{50}$ and $ED_{95}$ are 1.84 and 2.17 %, respectively [13], and the MAC value required for LMA insertion is greater than the MAC required for LMA removal [12]. Therefore, it appears that LMA insertion requires a depth of anesthesia greater than the recommended values in the first mentioned study.

A vital capacity inhalation induction technique with high-concentration sevoflurane has been used for the rapid and smooth insertion of LMA. However, some studies have reported that inhalation induction using sevoflurane alone caused coughing, excitatory movements, and prolonged time to jaw relaxation during LMA insertion despite high concentrations of sevoflurane of 4 or 8 % [1, 14, 15]. These results may be due to the fact that LMA insertion was performed without maintenance time of the end-tidal concentration of sevoflurane to allow for equilibrium of alveolar and brain sevoflurane partial pressure. The induction of anesthesia using high-concentration sevoflurane can also cause bradycardia or hypotension [2]. On the other hand, the addition of opioids to inhaled anesthetics can reduce autonomic and somatic responses to airway manipulation, decrease the requirement for inhalation drugs [16], and achieve more rapid and less eventful LMA insertion [17]. Therefore, combining opioids with volatile anesthetics is a good choice for achieving appropriate anesthetic conditions for LMA insertion.

The $ED_{50}$ and $ED_{95}$ values of remifentanil (0.176 and 0.268 μg/kg) for successful LMA insertion in the present study differed slightly from those when using intravenous induction of 2.5 mg/kg of propofol (0.52 and 0.71 μg/kg) in children [7]. The lower remifentanil doses in our study can be explained by the difference in the time of anesthesia maintenance to LMA insertion after the loss of consciousness of the patient. We provided sufficient time to reach equilibrium between alveolar and brain partial pressure by maintaining anesthesia with 2.1 % ETsevo for 10 min before LMA insertion. On the other hand, the insertion of LMA 70 s after a single injection of propofol [7] may not be satisfactory for successful insertion and, consequently, require a higher dose of remifentanil when considering that the time to peak effect of propofol was shown to be 132 s in children [18]. The other possible explanation is our use of intravenous midazolam for premedication. Premedication with midazolam can decrease coughing, gagging, and body movement during induction [19, 20]. Thus, it may reduce the effective dose of remifentnail required for LMA insertion in the present study.

Administration of an opioid is likely to cause bradycardia and hypotension, and it induces dose-dependent decreases in HR and BP. Therefore, administration of remifentanil over 30–60 s is recommended, and premedication with anticholinergic drugs at induction can be helpful for preventing adverse effects such as bradycardia [21]. An anticholinergic drug is also administered in cases in which the surgery induces vagal reflex stimulation such as in strabismus surgery [4]. In the present study, remifentanil was injected over 30 s and children were premedicated with atropine in order to prevent bradycardia and hypotension. As a result, although decreases in blood pressure were

observed immediately before and just after LMA insertion compared to baseline values, no patient experienced severe bradycardia or hypotension.

There are some limitations in this study. First, the estimated $ED_{50}$ and $ED_{95}$ of remifentanil are limited to the specific concentration of sevoflurane (2.1 % ETsevo). It is necessary to consider whether this dose of sevoflurane is appropriate for induction in children. The MAC and BIS have been used as measures of the anesthetic depth. The MAC of sevoflurane is 2.16–2.5 % in children between 1 and 12 years of age [5, 12]. A BIS range of 40–60 is recommended for maintaining unconsciousness during general anesthesia in adults [22]. Although the validity of the BIS in children is debatable, the BIS value is inversely proportional to ETsevo in children [23], so it can probably be used as an index of sedation in this age group. Tokuwaka et al. [24] reported that the MAC of sevoflurane required for maintaining the BIS below 50 in children aged 5–9 years was 2.1 %. The mean BIS score before LMA insertion was measured as 53.9 in the current study. Kwak et al. [7] reported that the $ED_{50}$ and $ED_{95}$ of remifentanil for LMA insertion in children during induction of anesthesia with 2.5 mg/kg propofol were 0.52 and 0.71 μg/kg, respectively. This means that the anesthetic depth achieved with 2.1 % sevoflurane may be deeper than that achieved with 2.5 mg/kg propofol. Therefore, considering that 2.5 mg/kg propofol is the recommended bolus dose for anesthesia induction in children [25, 26], the value of sevoflurane in the current study seems to be an adequate dose for induction in pediatric patients. Second, the wide age range among the children included in our study may have influenced the effective dose of remifentanil due to the age-related differences in volumes of distribution (Vd) and clearance rate (CL). However, remifentanil is an ultra-short-acting opioid with rapid metabolism by tissue and plasma esterase, and the function of the esterase appears mature at birth [5]. In addition, there are no age-dependent changes in body composition, which influence the apparent Vd for drugs, in children from the age of one upward [5]. In an age-related study of remifentanil pharmacokinetics, Rose et al. [27] also noted that the Vd, CL, and half-life did not change with age in children aged two and over.

In conclusion, the effective bolus doses of remifentanil for successful LMA insertion were 0.176 (0.168) and 0.268 μg/kg, respectively, in 50 and 95 % of children undergoing inhalation induction using 2.1 % sevoflurane without a neuromuscular blocking agent.

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