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Effective concentration of remifentanil for successful i-gel insertion during remimazolam induction

Jung Ju Choi, Wol Seon Jung, Young Jin Chang, Seungbeom Yoo, Hyun Jeong Kwak

Department of Anesthesiology and Pain Medicine, Gachon University Gil Medical Center, Incheon, South Korea

*Corresponding author: Hyun Jeong Kwack M.D., Ph.D.
Department of Anesthesiology and Pain Medicine
Gachon University Gil Medical Center
783 Namdong-daero, Namdong-gu, Incheon 21556, South Korea
Tel: 82-32-460-3624, Fax: 82-32-469-6319
E-mail: hyun615@gilhospital.com

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Abstract

Background: We evaluated the effective concentration (EC) of remifentanil effect-site concentration (Ce) for the successful insertion of an i-gel without neuromuscular blocking agents using the biased-coin up-and-down method in adult patients during remimazolam induction of 12 mg/kg/h.

Methods: Forty 19-65-year-old patients scheduled to undergo surgery using i-gel under general anesthesia were enrolled. Anesthesia was induced using an intravenous infusion of 12 mg/kg/h of remimazolam. Simultaneously, remifentanil was infused at a predetermined Ce. After 5 minutes of anesthesia induction, i-gel was inserted. The 95% EC (EC95) of remifentanil in each patient was determined using a biased-coined up-and-down method based on the successful insertion in a preceding patient, and the step size of remifentanil Ce was 0.4 ng/ml. If insertion failed, remifentanil Ce was increased in the next patient. Following successful insertions, the corresponding concentration was either decreased in the subsequent patient with a probability of 1/19 or maintained with a probability of 18/19. The time from initiating remimazolam infusion to a bispectral index (BIS) below 60 (time to BIS60) and hemodynamic variables were measured and recorded.

Results: The EC95 (95% confidence interval, CI) of remifentanil Ce was 2.07 (1.94–2.87) ng/ml. The overall time to BIS60 was 154.0 ± 39.9 s. No patient experienced significant hypotension or bradycardia during remimazolam induction.

Conclusions: The EC95 of remifentanil Ce for successful i-gel insertion without neuromuscular blocking agents was 2.07 (1.94–2.87) ng/ml during anesthetic induction with 12 mg/kg/h remimazolam in adult patients. Remimazolam induction could provide hemodynamic stability during i-gel insertion.

Keywords: Airway; General anesthesia; Intravenous anesthetics; Neuromuscular blocking agents;
Remimazolam; Remifentanil.
Introduction

I-gel, a type of supraglottic airway, is widely used to maintain the airway during outpatient anesthesia or emergency situations. I-gel is easier to insert and requires less tissue compression than other supraglottic airways with inflatable cuffs [1,2].

Propofol and midazolam are commonly used as intravenous anesthetic agents. However, propofol is associated with hemodynamic instability during anesthesia induction or infusion [3], and midazolam is associated with the delayed onset of drug action and delayed recovery [4]. Remimazolam is a recently introduced ultra-short-acting benzodiazepine that has a fast onset of action, is degraded by esterase, and has a stable context-sensitive time of 6-7 min even at various infusion times [5,6]. A recent randomized study showed that remimazolam induction (6 and 12 mg/kg/h) was not inferior to propofol induction (2 and 2.5 mg/kg) in terms of efficacy as a general anesthetic sedative [7].

When the operation does not require much muscle relaxation during general anesthesia, or when the operation time is short, the surgery can be performed with an airway secured by inserting a supraglottic airway without neuromuscular blockade for a quick recovery of the patient. A previous study has been reported that the use of neuromuscular blocking agents may affect the recovery of patients and delay the recovery of respiratory function [8]. However, to obtain sufficient anesthetic depth to decrease airway reactivity without neuromuscular blockade, the concentrations of sedatives should be increased to the level that may lead to hypotension and bradycardia. To avoid such complications, opioids can be concomitantly used as an adjuvant during anesthesia induction [9].

Depending on the type of sedative, the effective concentration (EC) of remifentanil effect-site concentration (Ce) for successful insertion during supraglottic airway insertion may vary. However, to date, no study has investigated the EC of remifentanil Ce for successful supraglottic
airway insertion during remimazolam induction. Thus, we evaluated the 95% EC (EC95) of remifentanil Ce for the successful insertion of i-gel without neuromuscular blocking agents using the biased-coin up-and-down method, and investigated the hemodynamic changes in adult patients during the induction of 12 mg/kg/h of remimazolam.
Materials and Methods

This study was approved by the institutional research ethics committee, registered at https://cris.nih.go.kr, and conducted following the receipt of informed consent from each patient after explaining the anesthetic procedure preoperatively. The inclusion criteria were an age between 19 and 65 years, American Society of Anesthesiologists (ASA) physical status 1 and 2, and scheduled surgery using i-gel as a supraglottic airway under general anesthesia. Exclusion criteria were patients who were allergic to the drugs used during this study, patients at high risk of aspiration, and patients expected to experience difficulty in intubation (limited mouth opening, cervical spine, extension restriction, or Mallampati class 4), and morbidly obese patients (body mass index >35 kg/m²).

After a patient arrived in the operating room without premedication, an electrocardiogram, non-invasive blood pressure, and pulse oximeter were installed, and a bispectral index (BIS) monitoring device (Covidien LLC, USA) was used to continuously measure the BIS and was attached to the frontal portion of the head. Patients were pre-oxygenated with 100% oxygen for 1 min, followed by an intravenous infusion of remimazoalm (12 mg/kg/h). Simultaneously, remifentanil was infused at a predetermined EC using a commercially available target-controlled infusion pump (Orchestra® Base Primea, Fresenius Kabi Company, France). After loss of consciousness (LOC), remimazoalm was maintained at 1 mg/kg/h. When consciousness and spontaneous breathing were lost, mask ventilation was performed with 100% oxygen. When it was confirmed that the BIS was below 60 after 5 minutes of anesthesia induction, i-gel (Intersurgical Ltd, Wokingham, Berkshire, UK) was inserted. Following the manufacturer's instructions, the anesthesiologist inserted the i-gel in a sniffing position by gently pushing it along the hard palate until resistance was felt. The success of i-gel insertion was defined as proper movement of the chest and a continual end-tidal CO₂ tension wave (without air leakage) at a peak airway pressure of < 20 cmH₂O. And we did not
apply PEEP (positive end expiratory pressure ventilation) in ventilator setting.

According to the biased-coined up-and-down method, the Ce of remifentanil in each patient was determined according to the successful insertion of the previous patient [10,11]. Assuming that the EC95 is determined ($\Gamma = 0.95$), the probability $B = 1 - \Gamma/\Gamma = 1 - 0.95/0.95 = 1/19$ is defined. The initial predetermined Ce of remifentanil was 1.5 ng/ml for the first patient because the starting dose should be the minimum dose expected to result in a positive response, i.e. close to the expected EC50 [12]. The step size was set as an increment or decrement of 0.4 ng/ml, since the interval between testing levels should be approximately equal to the standard deviation (SD) [12]. In a previous study, the estimated EC50 (SD) of remifentanil Ce for i-gel insertion during propofol induction using the Dixon’s up-and-down method was 1.58 (0.41) ng/ml [9]. If insertion failed, the remifentanil Ce was increased in the next patient. However, if the insertion was successful, the remifentanil Ce was either maintained with a probability of 18/19 or decreased with a probability of 1/19 in the next patient.

The depth of anesthesia was adjusted from a BIS value of 40 to 60, and the time from the start of remimazolam infusion to a BIS < 60 (time to BIS60) was recorded. Hemodynamic variables were measured and recorded before (baseline) and 1 min after induction of anesthesia and 1 and 5 min after i-gel insertion. Hypotension was defined as a systolic blood pressure decreased below 80 mmHg or decrease > 20% from baseline, and was treated with ephedrine (5 mg). Bradycardia was defined as a heart rate < 45 beats/min or decrease of >20% of baseline, and was treated with atropine (0.5 mg).

The simulation for sample size calculation demonstrated that 20–40 patients were required to obtain a target EC95 with a biased-coin up-and-down design [13]. Moreover, the non-independence and unknown distribution tendency of the up-and-down data requires theoretically conservative sample counting to calculate the required number of samples. Previous biased-coin
up-and-down studies have also demonstrated that a stable target dose can be obtained with 40 patients [14,15]. Therefore, only 40 patients were included in this study.

Statistical analyses were performed using IBM SPSS Statistics software version 23.0 (IBM Inc., USA) and R code for Windows version 3.2.2 (R foundation for statistical computing, Austria, Vienna). Data were presented as mean ± standard deviation, median [interquartile range], or number of patients. The normality of data distribution was tested using the Kolmogorov-Smirnov test. Comparisons of continuous data were analyzed using an independent t-test or a repeated measures analysis of variance as appropriate. The 90% EC (EC90) and EC95 for remifentanil Ce and their confidence intervals (CI) were estimated using an isotonic regression method with a bootstrapping approach [13,16]. The adjusted response probability was calculated using the pooled-adjacent-violators algorithm (PAVA) [8]. A P value < 0.05 was considered statistically significant.
Results

Forty patients were enrolled, all of whom completed the trial. Table 1 lists the patient characteristics, and Fig. 1 demonstrates the allocation sequence of remifentanil Ce according to the biased-coin up-and-down method. Eleven patients were allocated remifentanil at a Ce of 1.5 ng/ml, and the remaining patients were allocated remifentanil at a Ce ≥ 1.9 ng/ml (1.9 ng/ml, n = 24; 2.4 ng/ml, n = 5). Fig. 2 demonstrates the adjusted success rate from PAVA. The EC90 (95% CI) of remifentanil and EC95 (95% CI) were 1.86 (1.65–2.45) and 2.07 (1.94–2.87) ng/ml, respectively.

Table 2 lists the induction profiles and hemodynamic changes during remimazolam induction at 12 mg/kg/h. The induction profiles and hemodynamic changes were compared between the patients who were administered 1.5 ng/ml of remifentanil Ce and those who were administered higher than 1.9 ng/ml of remifentanil Ce (1.9 and 2.3), because 1.9 ng/ml of remifentanil Ce was closest to the EC95 value of 2.07 ng/ml in this study (Table 2). The overall time to BIS60 was 154.0 ± 39.9 s, and there were no statistical differences between patients receiving remifentanil Ce of 1.5 and ≥ 1.9 ng/ml. During remimazolam induction, no patients experienced significant hypotension or bradycardia. The changes in mean blood pressure and heart rate during induction were not significantly different between patients receiving remifentanil Ce of 1.5 and ≥ 1.9 ng/ml (P = 0.09 and 0.43, respectively).
Discussion

This study showed that the EC95 of remifentanil Ce was 2.07 (1.94–2.87) ng/ml for successful i-gel insertion without neuromuscular blocking agents during the induction of remimazolam at a dose of 12 mg/kg/h in adult patients. Moreover, remimazolam induction had a mean time to BIS60 of 154 s and provided hemodynamic stability during i-gel insertion.

Previous studies have reported various adjuvant drugs, including lidocaine, midazolam, and remifentanil, which enable supraglottic airway insertion with propofol as the induction agent [17]. However, no study has reported the effective concentration of remifentanil that enables supraglottic airway insertion using the newly developed drug remimazolam as an induction agent. Remimazolam is rapidly metabolized by carboxylesterases in the liver, and its metabolites have no pharmacological activity [18]. Furthermore, because the effect of remimazolam can be rapidly reversed by flumazenil, it may be safer to use than an inhalation agent or propofol used in the administration of conventional anesthesia [19].

A recent randomized study demonstrated that remimazolam was not inferior to propofol in its efficacy as a sedative for anesthesia induction [7]. In this study, anesthesia was induced by injecting remimazolam at a rate of 12 mg/kg/h. Several studies have been conducted to evaluate the EC50 or EC95 of remifentanil Ce, which enables i-gel or laryngeal mask airway (LMA) insertion during propofol induction without neuromuscular blockade. Jeon et al. [20] reported that, by applying Dixon’s up-and-down method, the EC95 of remifentanil for successful i-gel insertion was 2.44 and 0.75 ng/ml during 4.0 and 6 μg/ml of propofol induction, respectively, in patients who are expected to have difficult airways. Another study, which also applied Dixon's method, identified an EC95 2.38 ng/ml for remifentanil to enable i-gel insertion without the use of muscle relaxants during a propofol induction of 4.0 μg/ml effect-site concentration in female patients [9]. In this study, the EC95 (95% CI) of remifentanil for i-gel insertion was 2.07 (1.94–2.87) ng/ml
during an anesthetic induction of remimazolam at a dose of 12 mg/kg/h without neuromuscular blockade. This result is similar to the EC95 of remifentanil measured during induction at a 4.0 μg/ml propofol effect-site concentration reported in a previous study but showed a lower level.

The Dixon up-and-down method used in the studies described above was designed to determine EC50 by simplifying a biased-coin design, and this method can also be used for approximating EC95 by logistic or probit regression [10]. However, if the quartile is higher, the extrapolated EC95 obtained using the Dixon up-and-down method may impose significant bias [10]. By contrast, when a biased-coin design is adapted, EC can be estimated at any quartile [10]. In practice, the EC50 value of a drug for determining its dose is limited. This is because effectiveness should be achieved in 90–95% of patients, rather than only 50% [21]. Furthermore, when measuring the EC95 dose of a drug with a biased-coin design, the distribution of most administered doses tends to peak around the mean, and adverse effects that may occur with EC95 can be confirmed [13]. Therefore, in this study, a biased-coin design was used to approximate the EC95 of remifentanil for i-gel insertion without the use of muscle relaxants during induction with remimazolam.

In this study, stable hemodynamic conditions were maintained during induction and after i-gel insertion. No patient developed hypotension or bradycardia. The half-life of propofol is short, and recovery is rapid; however, it is associated with the potential for respiratory depression and hypotension [22]. According to a previous study, the occurrence of hypotension was lower with remimazolam than with propofol [7,22-24]. And, in patients with gastric cancer undergoing robotic gastrectomy, a significantly reduced amount of vasopressor was observed in the group anesthetized with remimazolam than in the group anesthetized with sevoflurane anesthesia, and a higher mean blood pressure was maintained intraoperatively [25]. Another study on patients undergoing colonoscopy reported a significantly lower incidence of hypotension in the group using
remimazolam than in the group using midazolam [26]. And, Chen et al [27] reported that the incidence of respiratory depression was significantly lower in the remimazolam group than in the propofol group [27]. Therefore, when using remimazolam during induction, i-gel insertion is expected to be possible while maintaining stable hemodynamics compared to conventional drugs.

This study has several limitations. First, because a fixed infusion rate of remimazolam was used, the effects of other remimazolam infusion rates and dosages on the effect-size concentrations of remifentanil could not be measured. Future studies should measure effect-size concentrations using remimazolam at various infusion rates and doses. Second, this study only included relatively healthy patients with ASA physical status 1 or 2 aged 19–65 years, and patients with various diseases and older patients might show a different hemodynamic response to the drug. Therefore, the results of this study may not be generalizable to all adults. However, our findings may also provide predictive indicators of drug demand in other patients. Third, although the time to the LOC is also one of the important characteristics of sedatives, we missed checking the time to LOC during remimazolam induction of 12 mg/kg/h.

In conclusion, the EC95 of remifentanil Ce for successful i-gel insertion without neuromuscular blocking agents was 2.07 (1.94–2.87) ng/ml during remimazolam induction at a dose of 12 mg/kg/h in adult patients. Moreover, remimazolam induction could provide hemodynamic stability during i-gel insertion.
References


21. Dennis Fisher. What if half of your patients moved (or remembered or did something else bad) at the incision? Anesthesiology 2007; 107: 1-2.


### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Remi1.5 (n = 11)</th>
<th>Remi≥1.9 (n = 29)</th>
<th>Total (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.1 ± 0.9</td>
<td>46.2 ± 11.2</td>
<td>47.0 ± 11.2</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>3/8</td>
<td>17/12</td>
<td>20/20</td>
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<tr>
<td>Weight (kg)</td>
<td>66.3 ± 13.0</td>
<td>68.3 ± 13.3</td>
<td>66.9 ± 13.5</td>
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<tr>
<td>Height (cm)</td>
<td>162.3 ± 8.3</td>
<td>166.2 ± 8.4</td>
<td>165.1 ± 8.5</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number of patients. Remi1.5: patients receiving remifentanil effect-site concentration (Ce) at 1.5 ng/ml; Remi≥1.9, patients receiving remifentanil Ce at 1.9 or 2.3 ng/ml.
Table 2. Comparison of Induction Profiles during Remimazolam Induction between Remifentanil Effect-site Concentrations

<table>
<thead>
<tr>
<th></th>
<th>Remi1.5 (n = 11)</th>
<th>Remi≥1.9 (n = 29)</th>
<th>Total (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success/failure</td>
<td>8/3</td>
<td>27/2</td>
<td>35/5</td>
</tr>
<tr>
<td>Time to BIS60 (s)</td>
<td>154.5 ± 48.4</td>
<td>153.8 ± 37.1</td>
<td>154.0 ± 39.9</td>
</tr>
<tr>
<td>Side effects during induction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>99.8 ± 15.5</td>
<td>104.6 ± 13.4</td>
<td>102.8 ± 14.5</td>
</tr>
<tr>
<td>T1</td>
<td>93.5 ± 13.5</td>
<td>98.4 ± 12.1</td>
<td>96.7 ± 12.9</td>
</tr>
<tr>
<td>T2</td>
<td>91.5 ± 13.5</td>
<td>88.9 ± 11.6</td>
<td>89.5 ± 12.2</td>
</tr>
<tr>
<td>T3</td>
<td>85.4 ± 10.8</td>
<td>81.6 ± 10.4</td>
<td>82.8 ± 10.7</td>
</tr>
<tr>
<td>Hear rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>71.9 ± 9.0</td>
<td>73.2 ± 12.0</td>
<td>72.0 ± 11.5</td>
</tr>
<tr>
<td>T1</td>
<td>74.1 ± 10.1</td>
<td>75.8 ± 14.5</td>
<td>75.4 ± 11.8</td>
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<tr>
<td>T2</td>
<td>75.3 ± 13.1</td>
<td>74.3 ± 11.0</td>
<td>74.6 ± 11.8</td>
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<tr>
<td>T3</td>
<td>76.3 ± 15.8</td>
<td>72.9 ± 10.7</td>
<td>74.8 ± 13.5</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number of patients. Remi1.5: patients receiving remifentanil effect-site concentration (Ce) at 1.5 ng/ml; Remi≥1.9, patients receiving remifentanil Ce at 1.9 or 2.3 ng/ml. Time to BIS60, Time from the start of remimazolam infusion to a bispectral index below 60. T0, before induction of anesthesia (baseline); T1, 1 min after induction of anesthesia; and T2 and T3, 1 and 5 min after i-gel insertion, respectively.
Fig. 1. The biased-coin up-and-down sequences of remifentanil effect-site concentration (Ce).

Success of i-gel insertion is represented by a filled circle, and failure of i-gel insertion is represented by an open diamond.
**Fig. 2.** Pooled-adjacent-violators algorithm response rate and remifentanil effect-site concentration (Ce). The 90% effective concentration and 95% effective concentration (95% confidence interval) were 1.86 (1.65–2.45) and 2.07 (1.94–2.87) ng/ml, respectively.