The optimal effect-site concentration of remifentanil for lightwand tracheal intubation during propofol induction without muscle relaxation

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**Abstract**

**Study Objective:** To determine the most suitable effect-site concentration of remifentanil during lightwand intubation when administered with a target-controlled infusion (TCI) of propofol at 4.0 μg/mL without neuromuscular blockade.

**Design:** Prospective study using a modified Dixon’s up-and-down method.

**Setting:** Operating room of an academic hospital.

**Patients:** 28 ASA physical status 1 and 2 patients, aged 18-65 years, scheduled for minor elective surgery.

**Interventions:** Anesthesia was induced by TCI propofol effect-site concentration to 4.0 μg/mL, and the dose of remifentanil given to each patient was determined by the response of the previously tested patient using 0.2 ng/mL as a step size. The first patient was tested at a target effect-site concentration of 4.0 ng/mL of remifentanil. If intubation was successful, the remifentanil dose was decreased by 0.2 ng/mL; if it failed, the remifentanil dose was increased by 0.2 ng/mL. Successful intubation was defined as excellent or good intubating conditions.

**Measurements and Main Results:** The remifentanil effect-site concentration was measured. The optimal effect-site concentration of remifentanil for lightwand tracheal intubation during propofol induction using 2% propofol target effect-site concentration to 4 μg/mL was 2.16 ± 0.19 ng/mL. From probit analysis, the effect-site concentration of remifentanil required for successful lightwand intubation in 50% (EC50) and 95% (EC95) of adults was 2.11 ng/mL (95% CI 1.16-2.37 ng/mL) and 2.44 ng/mL (95% CI 2.20-3.79 ng/mL), respectively.

**Conclusion:** A remifentanil effect-site concentration of 2.16 ± 0.19 ng/mL given before a propofol effect-site concentration of 4 μg/mL allowed lightwand intubation without muscle relaxant.

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1. Introduction

Lightwand tracheal intubation is a technique in which an illumination styllet is introduced into the endotracheal tube (ETT) and the tip of the ETT is directed into the trachea guided by transillumination of the neck tissues [1,2]. Lightwand tracheal intubation is a simple technique that is easily learned and may be useful if tracheal intubation by direct laryngoscopy is impossible [1]. Lightwand tracheal intubation has been recommended in the difficult airway algorithm of the ASA as an intubation choice for patients with difficult intubation and effective ventilation by face mask or Laryngeal Mask Airway (LMA; nonemergency pathway) [3]. The failure rate of lightwand tracheal intubation without a muscle relaxant is significantly higher than it is with a muscle relaxant [4]. Patients who are not first given a muscle relaxant undergo more intubation attempts, require greater intubation time, and experience a higher incidence of events during intubation than those who receive a muscle relaxant [4]. Tracheal intubation may be accomplished without muscle relaxants, but satisfactory conditions are not reliably obtained in all patients [5,6].

Remifentanil as part of an induction regimen provides good or excellent conditions for tracheal intubation without the need for muscle relaxants while attenuating the hemodynamic response to laryngoscopy [7]. Remifentanil also facilitates insertion of the LMA [8] and Cobra Perilaryngeal Airway (CobraPLA; Engineered Medical Systems, Inc., Indianapolis, IN, USA) [9]. The present study was designed to determine the most suitable effect-site concentration of remifentanil in providing successful lightwand tracheal intubation when given with a target-controlled infusion (TCI) of propofol at 4.0 μg/mL without neuromuscular blockade.

2. Materials and methods

After approval of the Institutional Review Board on Human Subjects Research and Ethics Committee of Hanyang University Guri Hospital and informed consent, ASA physical status 1 and 2 patients, aged 18-65 years, undergoing minor elective surgery, were considered for the study. Age, gender, weight, height, Mallampati class, mouth opening, and thyromental distance were recorded. Exclusion criteria included patients with cardiovascular, respiratory, hepatic, renal, or neuromuscular diseases; uncooperative patients; those with a history of gastroesophageal reflux or increased risk of aspiration; and those with coagulation disorders. Also excluded were patients with a history of difficult intubation or suspected difficult intubation, defined as a Mallampati class IV airway; retrognathia; restricted neck movements; or more than two criteria among the following: Mallampati class III airway, mouth opening less than 35 mm, or thyromental distance less than 65 mm. All of these parameters were measured by an experienced anesthesiologist.

In the operating room, routine monitors and a Bispectral Index sensor (BIS; Aspect Medical Systems, Norwood, MA, USA) were attached. Baseline values of mean arterial blood pressure (MAP), heart rate (HR), oxyhemoglobin saturation (SpO2), and BIS scores were recorded. These values were then measured at induction (loss of consciousness), intubation, and one minute after intubation. After each patient received 100% oxygen by face mask, anesthesia was induced by TCI propofol using the pharmacokinetic (PK) parameter set of Schneider et al [10], as included in the Orchestra Base Primea infusion device (Fresenius Kabi, Bad Homburg, Germany), and by setting the propofol target effect-site concentration to 4.0 μg/mL. Propofol effect-site concentrations were determined on the basis of an equilibration constant (Keo) of 0.456/min. Before administration of propofol, remifentanil was given by a TCI device to ensure a constant effect-site concentration. The Orchestra Base Primea infusion device, whose PK was the Minto et al model [11], which adjusts for age, weight, and gender, and has a Keo of 0.595-0.007×(age-40)/min, was used.

The dose of remifentanil given to each patient was determined by the response of the previously tested patient using a modified Dixon’s up-and-down method (using 0.2 ng/mL as a step size) [12]. The first patient was tested at a target effect-site concentration of 4.0 ng/mL of remifentanil. If intubation was successful, the remifentanil effect-site concentration was decreased by 0.2 ng/mL; if it failed, the concentration was increased by 0.2 ng/mL.

During administration of propofol and remifentanil, patients were asked to open their eyes every 10 seconds. Failure to do so was taken as loss of consciousness, and was confirmed by testing the loss-of-eyelash reflex. BIS score, propofol effect-site concentration, and remifentanil concentration were checked at the same time. After the BIS score decreased below 60, the propofol effect-site concentration was greater than 4.0 μg/mL, and the remifentanil effect-site concentration reached a determined level, all patients underwent direct laryngoscopy without intubation by another anesthesiologist who was blinded to the previous measurements. Views were scored according to Cormack and Lehane criteria [13].

Lightwand tracheal intubation with the Surch-Lite (Aron Medical, St. Petersburg, FL, USA) was attempted by an anesthesiologist with more than 50 previous intubations; the lightwand with Surch-Lite was used after the BIS value was again below 60. All procedures were performed by the same anesthesiologist (CS). The patient’s head and neck were placed in a neutral position during ambient light conditions, with the lightwand bent at a 90° angle. Endotracheal tubes with a 7.5 mm and 7.0 mm internal diameter for men and women, respectively, were used. Any intubation attempt that lasted more than two minutes or was associated with the appearance of cough, patient movement, peripheral SpO2...
less than 92%, or esophageal intubation was stopped. Total intubation time and events during the whole procedure were recorded. Total intubation time was defined as the interval between insertion of the Surch-Lite into the oral cavity and verification of tracheal intubation with visualization of three expiratory CO₂ waveforms.

Failure to intubate was defined as the inability to place the ETT into the trachea. In these cases, rocuronium 0.6 mg/kg was administered; intubation was performed following neuromuscular blockade.

2.1. Statistics

Statistical analysis was performed using the Statistical Package for Social Sciences Software (SPSS 12.0 for windows; SPSS Inc., Chicago, IL, USA) and SigmaStat, version 3.1 (Systat Software, Inc., Chicago, IL, USA). The effect-site concentration of remifentanil required for successful lightwand intubation in 50% of adults (EC50) was determined by calculating the midpoint concentration of all independent pairs of patients after at least 7 crossover points (ie, failure of success with lightwand intubation) were obtained. The EC50 and EC95, with 95% confidence intervals (CI), were determined by probit analysis.

Hemodynamic data were analyzed with repeated-measures analysis of variance. A P-value < 0.05 was considered statistically significant.

3. Results

Twenty-eight patients were enrolled in this study; demographic data are shown in Table 1. Dose-response data for each patient obtained by the up-and-down method are shown in Fig. 1. The optimal effect-site concentration of remifentanil for lightwand tracheal intubation during propofol induction using 2% propofol target effect-site concentration to 4 µg/mL was 2.16 ± 0.19 ng/mL. From probit analysis, the EC50 and EC95 were 2.11 ng/mL (95% CI 1.16-2.37 ng/mL) and 2.44 ng/mL (95% CI 2.20-3.79 ng/mL), respectively.

The characteristics of successful lightwand intubation are shown in Table 2. The rate of successful lightwand intubation conditions was 75% (21/28), and total intubation time was 54.8 ± 37.0 seconds. The total dose of propofol at successful lightwand intubation was 132.5 ± 28.1 mg. The average BIS value on successful lightwand intubation was 57.3 ± 13.9.

Mean arterial pressure and HR with successful lightwand intubation patients are shown in Table 3. Mean arterial pressure at induction was significantly decreased compared with baseline values, and MAP recorded one minutes after intubation returned to baseline values. There were no significant differences in HR values among baseline values, at induction, and one minute after intubation.

4. Discussion

A remifentanil effect-site concentration of 2.16 ± 0.19 ng/mL administered before a propofol effect-site concentration of 4.0 µg/mL allowed for successful lightwand intubation without muscle relaxant.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic data</th>
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<tbody>
<tr>
<td>Gender M:F</td>
<td>13 : 15</td>
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<tr>
<td>Age (yrs)</td>
<td>42.9 ± 15.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.5 ± 9.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.8 ± 9.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0 ± 2.9</td>
</tr>
<tr>
<td>Mouth opening (cm)</td>
<td>4.6 ± 0.8</td>
</tr>
<tr>
<td>TMD (cm)</td>
<td>7.5 ± 1.2</td>
</tr>
<tr>
<td>Cormack-Lehane classification (I/II/III/IV)</td>
<td>15/6/7/0</td>
</tr>
</tbody>
</table>

Values are means ± SD or numbers of patients. BMI = body mass index, TMD = thyromental distance.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Characteristics of successful lightwand intubation</th>
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<tbody>
<tr>
<td>Successful intubation (success/total)</td>
<td>21/28</td>
</tr>
<tr>
<td>Total intubation time (sec)</td>
<td>54.8 ± 37.0</td>
</tr>
<tr>
<td>Dose of propofol (mg)</td>
<td>132.5 ± 28.1</td>
</tr>
<tr>
<td>Dose of remifentanil (µg)</td>
<td>169.5 ± 245.7</td>
</tr>
<tr>
<td>BIS</td>
<td>57.3 ± 13.9</td>
</tr>
</tbody>
</table>

Values are means ± SD or numbers of patients. BIS = Bispectral Index.
Remifentanil is a potent opioid with rapid onset and ultrashort duration of action [11,14]. In healthy outpatients, bolus administration of remifentanil provided effective control of the acute hemodynamic response to tracheal intubation with [7] and without muscle relaxants [5,6]. In children, Min et al [15] showed that the optimal bolus dose of remifentanil for successful tracheal intubation was 0.56 μg/kg in 50% of children during inhalation induction using 5% sevoflurane in oxygen without neuromuscular blocking agents. Park et al [16] found that the coadministration of remifentanil halved propofol requirements and improved insertion conditions for LMAs and laryngeal tubes in children. Jeon et al [9] showed that a remifentanil effect-site concentration of 2.0 ng/mL administered before a propofol effect-site concentration of 6 μg/mL created excellent conditions for insertion of the CobraPLA on the first attempt with minimal hemodynamic disturbances.

Target-controlled infusion systems deliver intravenous (IV) drugs on the basis of PK models. In this study, we used the Orchestra Base Primea infusion device, which enabled administration of propofol, sufentanil, and remifentanil on the basis of effect-site TCI [17]. The Orchestra Base Primea has been established by clinical studies [10,11,18].

The effect-site concentration is the estimation of the concentration in a fourth compartment that represents the organ where the drug is active. This compartment is virtually linked to a central compartment with partition coefficient (Keo). The Orchestra Base Primea allows the user to target the effect-site concentration. This is different from the plasma concentration control as it permits an overshoot in the plasma concentration allowing rapid achievement of the desired effect-site concentration. Struys et al [19] also showed that a TCI device which controlled the concentration at the site of drug effect more accurately produced the desired time course of drug effect than did a device which controlled only plasma concentration.

Massó et al [4] reported that total intubation time in the rocuronium group was 52 ± 31 seconds and 77 ± 6 seconds in the placebo group; the total dose of remifentanil in the rocuronium group was 96 ± 31 μg and in the placebo group it was 117 ± 60 μg. In this study, total intubation time was 54.8 ± 37.0 seconds, and the total dose of remifentanil administered was 169.5 ± 245.7 μg. The difference in total intubation time between Massó et al’s placebo group and our group may have been due to the difference in total dose of remifentanil (117 ± 60 μg vs 169.5 ± 245.7 μg).

In principle, avoiding direct-vision laryngoscopy may allow for less stimulation by intubation than the conventional laryngoscopic procedure. However, whether the hemodynamic responses to intubation with laryngoscopy differ from those with direct laryngoscopy is controversial [20,21]. Takahashi et al [20] showed that hemodynamic responses to tracheal intubation with a laryngoscope did not differ from those with a direct laryngoscope during sevoflurane anesthesia. It was likely that direct stimulation of the trachea by an ETT had a major role in causing the cardiovascular responses to tracheal intubation in the sevoflurane-anaesthetized patients. Conversely, Nishikawa et al [21] confirmed that in normotensive patients a laryngoscope technique is accompanied by a smaller increase in systolic blood pressure after tracheal intubation than with the laryngoscopic technique.

Our study has a number of limitations. First, we used a modified Dixon’s up-and-down method. This study design is a good technique to determine EC50, but it is less powerful in determining EC95. Second, all intubations were performed by an experienced anesthesiologist, and our findings may not be applicable to less experienced users. Finally, we used only the 4.0 μg/mL dose of propofol effect-site concentration; if we had chosen another effect-site concentration, such as 3.0 or 6.0 μg/mL, there would have been a synergistic effect between the propofol and remifentanil.

In conclusion, the effect-site concentration of remifentanil for successful lightwand intubation for 50% of adults was 2.16 (SD 0.19) ng/mL during induction using a TCI of 4.0 μg/mL of propofol without a neuromuscular blocking agent. From probit analysis, the EC50 and EC95 were 2.11 ng/mL (95% CI 1.16-2.37 ng/mL) and 2.44 ng/mL (95% CI 2.20-3.79 ng/mL), respectively.

### Table 3 Mean arterial pressure (MAP) and heart rate (HR) during Induction

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Induction</th>
<th>One min after intubation</th>
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<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>96.6 ± 14.9</td>
<td>86.1 ± 15.2 *</td>
<td>87.5 ± 15.2</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>73.6 ± 13.1</td>
<td>70.1 ± 10.6</td>
<td>79.6 ± 12.7</td>
</tr>
</tbody>
</table>

Values are means ± SD. * P < 0.05 vs baseline values.

References


