



Optimal effect-site concentration of remifentanyl to prevent hemodynamic changes during nasotracheal intubation using a video laryngoscope

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Background: Nasotracheal intubation is the most commonly used method to secure the field of view when performing surgery on the oral cavity or neck. Like orotracheal intubation, nasotracheal intubation uses a laryngoscope. Hemodynamic change occurs due to the stimulation of the sympathetic nervous system. Recently, video laryngoscope with a camera attached to the end of the direct laryngoscope blade has been used to minimize this change. In this study, we investigated the optimal effect-site concentration (C_e) of remifentanyl for minimizing hemodynamic responses during nasotracheal intubation with a video laryngoscope.

Methods: Twenty-one patients, aged between 19 and 60 years old, scheduled for elective surgery were included in this study. Anesthesia was induced by slowly injecting propofol. At the same time, remifentanyl infusion was initiated at 3.0 ng/ml via target-controlled infusion (TCI). When remifentanyl attained the preset C_e , nasotracheal intubation was performed using a video laryngoscope. The patient's blood pressure and heart rate were checked pre-induction, right before and after intubation, and 1 min after intubation. Hemodynamic stability was defined as an increase in systolic blood pressure and heart rate by 20% before and after nasotracheal intubation. The response of each patient determined the C_e of remifentanyl for the next patient at an interval of 0.3 ng/ml.

Results: The C_e of remifentanyl administered ranged from 2.4 to 3.6 ng/ml for the patients evaluated. The estimated optimal effective effect-site concentrations of remifentanyl were 3.22 and 4.25 ng/ml, that were associated with a 50% and 95% probability of maintaining hemodynamic stability, respectively.

Conclusion: Nasotracheal intubation using a video laryngoscope can be successfully performed in a hemodynamically stable state by using the optimal remifentanyl effect-site concentration (C_{e50} , 3.22 ng/ml; C_{e95} , 4.25 ng/ml).

Keywords: Effect-Site Concentration; Nasotracheal Intubation; Remifentanyl; Video Laryngoscopes.

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INTRODUCTION

Nasotracheal intubation (NTI) is the most commonly

used method of anesthesia for head and neck surgery. NTI passes the tracheal tube through the nose, which allows easy access to the intraoral lesion, enabling efficient oral surgery [1]. However, NTI can make a

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patient hemodynamically unstable. Increased blood pressure and heart rate (HR) may increase the risk of arrhythmia, myocardial infarction, and cerebral hemorrhage [2].

Moreover, intubation using a direct laryngoscope requires the patient to be in a ‘sniffing position’ by extending the upper cervical spine and flexing the lower cervical spine. Intubation may be challenging due to limited neck flexion, narrow jaw opening, large tongue, cervical instability, and poor tissue mobility [3]. During a scheduled intubation, these can occur in 1 to 6% of cases [4]. Failed or difficult intubation can result in raised blood pressure, increased risk of desaturation, unexpected care in intensive care unit, or death [5-7].

As an alternative to direct laryngoscopes, several technologies, including fiberoptic, are being introduced to aid intubation. Since the early 2000s, various types of video laryngoscopes have been developed to solve the problem of difficult intubations [8]. KoMAC Video Laryngoscope (KoMAC Co, Ltd, Seoul, Republic of Korea) is used for endotracheal intubation to secure the airway during emergencies or general surgery. It is easier and safer than the previous intubation method because it is performed by looking at the image of the oral cavity through a monitor. Disposable blades can be used to prevent cross-infection.

Remifentanyl is a potent opioid that is selective for the μ -receptor. Remifentanyl has a fast expression time and a short action time in which it is hydrolyzed by nonspecific esterase in blood and tissue. It has a context-sensitive half-life of about 3 min. Therefore, it is widely used for general anesthesia as it allows fast and sufficient sympathetic blockage during endotracheal intubation [9].

To this end, we calculated the concentration of remifentanyl needed to minimize cardiovascular changes during airway intubation with a video laryngoscope, and the administration of desflurane in healthy Korean patients who had undergone dental surgery. We also wanted to evaluate whether there was a difference in remifentanyl concentrations needed between men and women.

Table 1. Demographic data

	Data
Number of patients	21
Sex (M/F)	13/8
Age (yr)	37.4 \pm 14.9
Weight (kg)	66.7 \pm 6.56
Height (cm)	168.7 \pm 8.76
ASA class (I/II)	16/5

The values are number of patients or the mean \pm SD. ASA, American Society of Anesthesiologists.

METHODS

This study was approved by the Institutional Review Board of Pusan National University Dental Hospital, Yangsan, Korea (IRB No. PNUDH-2019-039). Patients who participated in this study signed an informed consent form. Twenty-one American Society of Anesthesiologists (ASA) Physical Status I or II patients, aged between 19 and 60 years old, who were scheduled for elective surgery at Pusan National University Dental Hospital were included in this study. The patients with cardiovascular, pulmonary, hepatic, or renal disease were excluded from this study (Table 1).

Thirty minutes before arrival in the operating room, 0.2 mg of glycopyrrolate was administered by an intramuscular injection. A 20-gauge intravenous angiocatheter was inserted in the patient’s forearm. After the patient entered the operating room, a non-invasive blood pressure (NBP) measurement device, electrocardiography, pulse oximetry, and a bispectral index (BIS) monitoring device (BIS-XP monitor, Aspect Medical Systems Inc., Natick, Massachusetts, USA) were connected to the patient. Electrocardiography, HR, oxygen saturation, and BIS were continuously monitored from when the patient arrived in the operating room to the end of surgery. NBP was measured every 5 min during the procedure [10].

After 5 min of oxygenation with 100% oxygen, propofol 2 mg/kg was slowly injected into the patient’s vein. At the same time, remifentanyl, which was diluted in 50 ml saline to a concentration of 20 mcg/ml, was started at 3 ng/ml via a commercial target-controlled

Table 2. Hemodynamic changes

	T0	T1	T2	T3
SBP (mmHg)	130.2 ± 16.32	99.76 ± 12.51	126.8 ± 20.64	118 ± 12.47
MBP (mmHg)	93.76 ± 10.99	74.57 ± 10.24	97.52 ± 14.53	89.76 ± 9.62
HR (beats/min)	76.71 ± 21.28	75 ± 12.13	85.33 ± 12.28	84.71 ± 11.3
SpO ₂ (%)	99 ± 1	99.52 ± 0.6	99.57 ± 0.51	99.52 ± 0.51
BIS	93.9 ± 4.4	44.52 ± 5.58	43.71 ± 5.98	42.05 ± 5.6

Values are mean ± SD. MBP, mean blood pressure; HR, heart rate; SpO₂, oxygen saturation; T0, baseline; T1, before nasotracheal intubation; T2, right after nasotracheal intubation; T3, 1 min after nasotracheal intubation.

infusion (TCI) machine (Injectomat TIVA Agilia, Fresenius Kabi, Bad Homburg, Germany) using the Minto's pharmacokinetic model [11]. When the patient lost consciousness, the dial of the desflurane vaporizer was set at a 1 MAC concentration with mask-assisted ventilation. Mapleson's equation ($MAC_{age} = MAC_{40} \times 10^{-0.00269(age-40)}$) was used to calculate 1 MAC. The age-corrected MAC value is MAC_{age}; for example, 1 MAC for a 40-year-old patient is MAC₄₀. Then, 0.6 mg/kg rocuronium was injected, and when remifentanil reached its predetermined concentration, nasotracheal intubation was performed using a video laryngoscope. The systolic blood pressure (SBP), diastolic blood pressure, mean blood pressure (MBP), HR, oxygen saturation (SpO₂), end-tidal concentrations of desflurane, and BIS were checked at different time points, such as when the remifentanil infusion started (baseline, T0), before nasotracheal intubation (T1), right after nasotracheal intubation (T2), and 1 min after nasotracheal intubation (T3). We prepared 0.1 mg/kg ephedrine for hypotension (MBP < 50 mmHg) and 0.01 mg/kg atropine for bradycardia (HR < 50) in case of side effects from the remifentanil or desflurane. The remifentanil infusion was initiated at a dose of 3 ng/ml. When comparing T1 and T2, if a patient's SBP and HR increased by more than 20%, which was considered as hemodynamic instability, the target concentration of remifentanil for the next patient was increased by 0.3 ng/ml. If a patient's vital sign did not exceed 20%, we considered this hemodynamic stability; the target concentration of remifentanil for the next patient was decreased by 0.3 ng/ml [12,13]. All intubation was performed by one anesthesiologist.

Using the observation of stable and unstable hemodynamics after nasotracheal intubation, every effect-site concentration of remifentanil was joined to 0 (hemodynamic instability) or 1 (hemodynamic stability). Hemodynamic stability was defined as an increase in systolic blood pressure and heart rate below 20% before and after nasotracheal intubation. The relationship between the probability of maintaining hemodynamic stability (P [hemodynamic stability]) and the effect-site concentration of remifentanil was analyzed using a sigmoid Emax model:

$$P(\text{Hemodynamic stability}) = \frac{C_e^\gamma}{C_{e50}^\gamma + C_e^\gamma}$$

where C_e is the effect-site concentration of remifentanil, C_{e50} is the effect-site concentration of remifentanil associated with a 50% probability of maintaining hemodynamic stability, and γ is the steepness of the concentration-vs.-response relation. The likelihood, L , of the observed response on the hemodynamic stability, R , is described by the following equation:

$$\text{Likelihood} = R \times \text{Prob} + (1 - R) \times (1 - \text{Prob}) \quad (2),$$

where Prob is the probability of maintaining hemodynamic stability.

The logistic regression was performed using NONMEM[®] 7 level 4 (ICON Development Solutions, Dublin, Ireland). Inter-individual variations could not be successfully estimated with only one point per individual. Therefore, a naïve-pooled data approach was used. Model parameters were estimated using the option "LIKELIHOOD LAPLACE METHOD=conditional" of NONMEM [14] (Appendix).

RESULTS

Twenty-three patients participated in this study, but two of them were excluded due to hypotension after propofol injection. Each patient's SBP, MBP, HR, SpO₂, and BIS were measured at different times (Table 2). All nasotracheal intubations were successful without complications, such as oxygen desaturation (SpO₂ under 90%), bradycardia (HR slower than 50 beats/min), or hypotension (MBP below 50 mmHg). Ten of the 21 patients were classified into the 'hemodynamic stability' group, and the other 11 were included in the 'hemodynamic instability' group. We compiled a graph showing the concentration of remifentanyl administered to each patient (Fig. 1), and their SBP, and HR were measured (Fig. 2).

We found the *C_e* of remifentanyl required to minimize cardiovascular changes during nasotracheal intubation

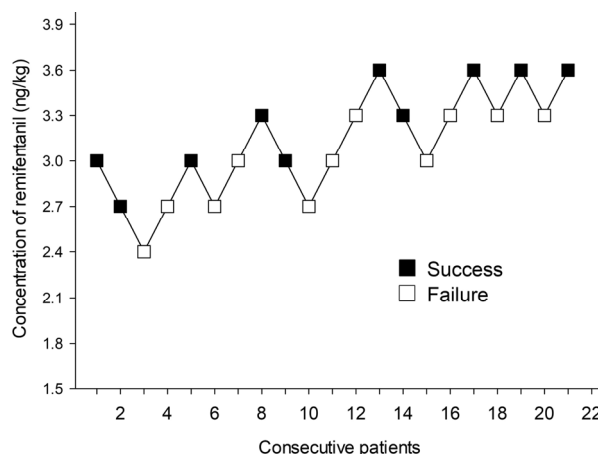


Fig. 1. Consecutive patients in hemodynamic stability group (S) and hemodynamic instability group (F). The "S" group was defined as less than a 20% change in heart rate (HR) and systolic blood pressure (SBP) at just after tracheal intubation compared to those of just before tracheal intubation. If a patient's HR or SBP change exceeded 20%, then they were assigned to the "F" group. If the patient belongs to the "S" group, the target concentration of remifentanyl for the next patient was decreased by 0.3 ng/ml. When the patient's vital sign meets the "F" group's criteria, the target concentration of remifentanyl for the next patient was increased by 0.3 ng/ml.

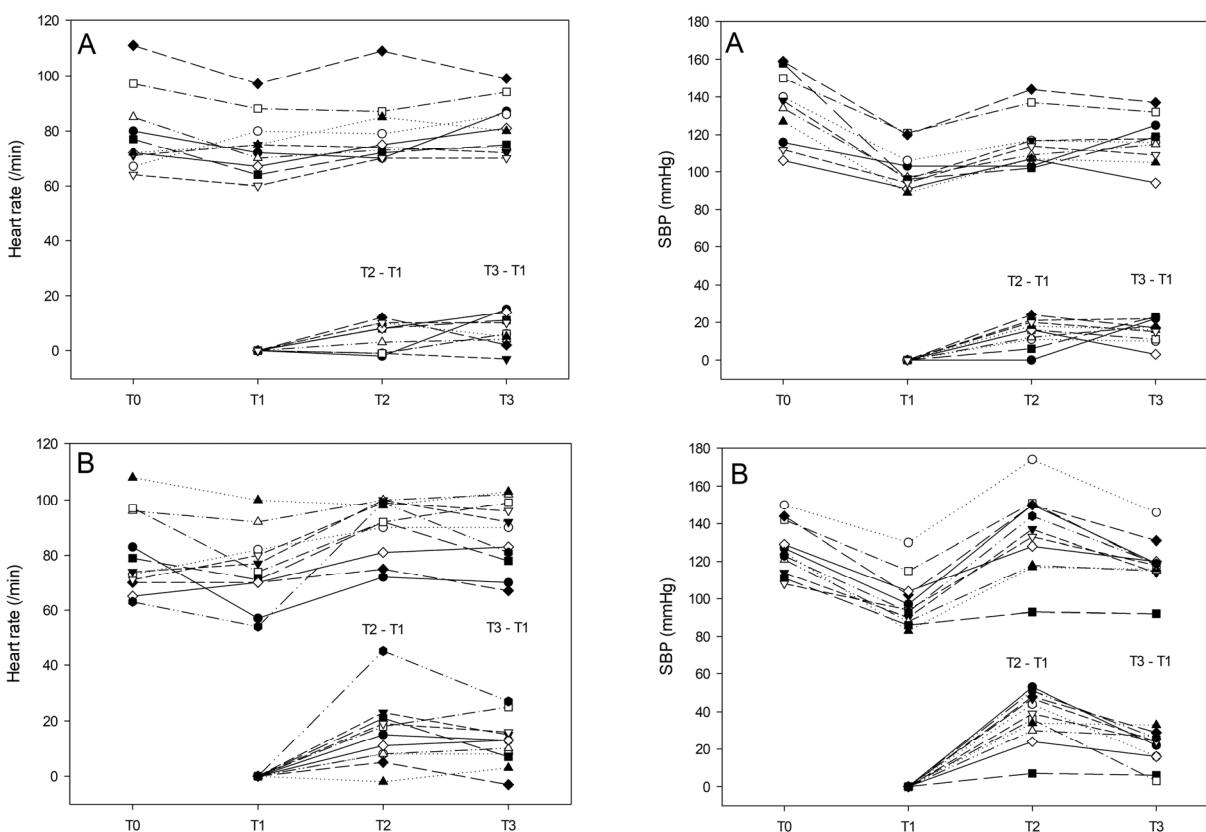


Fig. 2. Changes in heart rate (HR) and systolic blood pressure (SBP) of each patient in the 'hemodynamic stability' group (A) and 'hemodynamic instability' group (B). T0: baseline, T1: before nasotracheal intubation, T2: just after nasotracheal intubation, T3: 1 min after nasotracheal intubation.

with a video laryngoscope. The calculated effect-site concentration of remifentanyl associated with a 50% and 95% probability of maintaining hemodynamic stability were 3.22 and 4.25 ng/ml, respectively (Fig. 3). Population pharmacodynamic parameter estimates and optimal parameter values (2.5-97.5%) of the non-parametric bootstrap replicates of the final pharmacodynamic model for the probability of maintaining hemodynamic stability after nasotracheal intubation were also calculated (Table 3).

The *Ce₅₀* of remifentanyl for men and women was 3.19 and 3.27 ng/ml, respectively. There was no statistically significant difference between males and females.

DISCUSSION

Remifentanyl has been widely used as an adjuvant

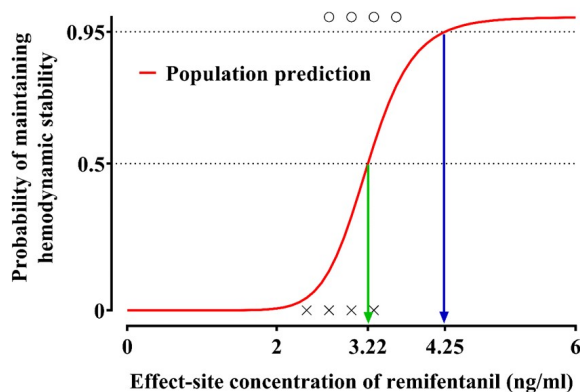


Fig. 3. Predicted probability of maintaining hemodynamic stability plotted against effect-site concentrations of remifentanyl. X: effect-site concentration of remifentanyl when hemodynamic instability was observed, O: effect-site concentration of remifentanyl when hemodynamic stability was observed. Red solid line indicates population prediction. The estimates of effect-site concentration of remifentanyl associated with 50% and 95% probability of maintaining hemodynamic stability were 3.22 and 4.25 ng/ml, respectively.

anesthetic drug because of its fast onset time, absence of accumulation even when continuously injected, and short context-sensitive half-time [15]. Pharmacokinetic models for the continuous infusion of intravenous anesthetics have been used because remifentanyl is challenging to measure in blood, and its bolus injection can cause side effects such as hypotension and bradycardia. Representative pharmacokinetic models of remifentanyl have been reported by Minto et al. [16]. In recent years, many studies have examined the concentration of remifentanyl to minimize hemodynamic changes during endotracheal intubation. In previous studies, the *Ce₅₀* values of remifentanyl associated with direct laryngoscope were 5.58 ± 0.75 and 6.08 ± 0.75 ng/ml for orotracheal and nasotracheal intubation, respectively, with propofol at a target effect-site concentration of $5.0 \mu\text{g/ml}$ [17]. This study found that the cardiovascular response to NTI is significantly greater than that of orotracheal intubation. This is because NTI produces greater mechanical stimulation of the upper airway as the nasotracheal tube is passed through the nose and nasopharynx, resulting in a stronger activation of the sympathetic nervous system and causing an increase in HR and blood pressure [18,19].

Another study said that when orotracheal intubation is performed with 1 MAC desflurane, the *Ce₅₀* of remifentanyl during orotracheal intubation was 3.7 ng/ml [20]. The difference of remifentanyl concentration in orotracheal intubation depends on whether the intravenous or inhalational agent was used. Mahli et al. [21] reported that the values of mean arterial pressure (MAP) and HR for the propofol group were significantly higher than the desflurane group during general anesthesia.

Ithnin et al. [22] showed that the *Ce₅₀* of remifentanyl

Table 3. Population pharmacodynamic parameter estimates and optimal parameter values (2.5-97.5%) of the non-parametric bootstrap replicates of the final pharmacodynamic model for the probability of maintaining hemodynamic stability after nasotracheal intubation

Parameters	Estimates (SE)	RSE (%)	Range (2.5-97.5%)
<i>Ce₅₀</i> (ng/ml)	3.22 (0.15)	4.6	3.24 (3.02-3.40)
γ	10.6 (5.23)	49.3	12.4 (5.3-102.0)

inter-individual random variability was assumed. Non-parametric bootstrap analysis was repeated 2000 times. RSE, relative standard error = SE/mean $\times 100$ (%); *Ce₅₀*, effect-site concentration of remifentanyl associated with a 50% probability of maintaining hemodynamic stability after nasotracheal intubation; γ , the slope steepness for the relationship of the effect-site concentration of remifentanyl versus response.

required for orotracheal intubation with the Macintosh video laryngoscope was 4.41 ng/ml, and that of the Glidescope (direct laryngoscope) was 5.45 ng/ml with propofol TCI at a target effect-site concentration of 3.0 μ g/ml.

We wanted to determine the hemodynamic changes that occur in patients undergoing NTI using video laryngoscope and the CE_{50} of remifentanyl with inhalation anesthetics. Lee et al. [23] indicated that remifentanyl was safe and effective at a target C_e of 4 ng/ml. In this study, due to concerns that the side effects of the propofol injection (such as hypotension) may be elevated, we started to administer remifentanyl at 3 ng/ml in the first patient.

Based on the previous studies, we found that using a video laryngoscope required a lower concentration of remifentanyl than a direct laryngoscope for hemodynamically stable NTI. Video laryngoscope is mainly used for difficult intubation; however, it may help to minimize the sympathetic nervous system response during endotracheal intubation even in patients with normal anatomical airway structures.

There are some limitations to this study. First, after the bolus injection of propofol, inhalation of desflurane was started. This means that propofol has the potential to offset the effects of desflurane on patients during intubation. Second, there is no difference in the remifentanyl concentration between men and women. To calculate statistically significant values, we needed a sample size of between 20 and 40 [23]. However, we only had 13 and 8 samples for men and women, respectively. The statistical accuracy of this study might be improved with a bigger sample size.

In conclusion, the CE_{50} and CE_{95} of remifentanyl to minimize the cardiovascular changes to NTI during 1 MAC desflurane anesthesia with a video laryngoscope were 3.22 ng/ml and 4.25 ng/ml, respectively. During anesthesia with desflurane and a remifentanyl infusion, patients had cardiovascular stability and no complications.

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Eun-Jung Kim: Data curation, Methodology
Byung-Moon Choi: Formal analysis
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Yeon Ha Kim: Visualization
Moon Ok Lee: Data curation
Ki Seob Han: Methodology
Ji-Hye Ahn: Writing - review & editing

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Appendix. Example of the control stream used in the pharmacodynamic modeling

```
$PROB RUN# 601 (Logistic Regression)
$DATA Nasotracheal_intubation_YJW.csv IGNORE=#
$INPUT ID OID CE DV MDV AGE SEX

$PRED

  TH1 = THETA(1)
  TH2 = THETA(2)

  GAM = TH1*EXP(ETA(1))
  CE50 = TH2*EXP(ETA(2))

  PROB = CE**GAM/(CE50**GAM+CE**GAM)
  Y = DV*PROB+(1 - DV)*(1 - PROB)
  IPRED = Y
  W = 1
  IRES = DV - IPRED
  IWRES = IRES

$THETA; #2
  (1, 3); GAM
  (0, 1); CE50

$OMEGA; #0
  0 FIX ; IIV_GAM
  0 FIX ; IIV_CE50

$ESTIMATION MAX=9999 SIGL=6 NSIG=2 LIKELIHOOD LAPLACE PRINT=5 NOABORT METHOD=1
$COVARIANCE PRINT=E

$TABLE ID ETA(1) ETA(2)
  FILE=601.ETA NOPRINT FIRSTONLY NOAPPEND ; fit4NM, PDx pop
$TABLE ID GAM CE50
  FILE=601.PAR NOPRINT ONEHEADER FIRSTONLY NOAPPEND ; fit4NM, PDx pop
```