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The target concentration of remifentanil to suppress the hemodynamic response to endotracheal intubation during inhalational induction with desflurane

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Background: Anesthesia induction with desflurane is troublesome because of the frequent sympathetic hyperactivity during desflurane administration. We thought that a low concentration of desflurane combined with a target-controlled infusion (TCI) of remifentanil would eliminate the desflurane-related complications and provide hemodynamic stability during desflurane induction. An up-and-down study was planned to find the target effect-site concentration of remifentanil to block the hemodynamic response to endotracheal intubation, the highest level of stimulus, during anesthesia induction with administering desflurane at 1 MAC.

Methods: Remifentanil TCI was initiated before desflurane administration. When the preset target was achieved, spontaneous inhalation of desflurane 1 MAC was performed until the patients became unconscious. Laryngoscopic tracheal intubation was facilitated with rocuronium injection. The starting concentration of remifentanil and the test space were 5 and 1 ng/ml, respectively. The criteria for up-and-down was a 20% increase of the mean arterial pressure or heart rate after intubation. The median effective concentration (EC_{50}) of remifentanil was calculated from 6 independent pairs. The complications related with remifentanil and desflurane were assessed during the study.

Results: We studied 20 patients using 2−5 ng/ml of the effect-site concentrations of remifentanil. The EC_{50} of remifentanil was 3.7 ng/ml. Loss of consciousness was achieved at 125 ± 22 s after desflurane inhalation and this was irrespective of the combined remifentanil concentrations. Any remifentanil-related complication was not observed. Transient cough was seen in one patient who received 2 ng/ml of remifentanil.

Conclusions: We demonstrated that uncomplicated induction with desflurane was possible by the use of target-controlled remifentanil. The EC_{50} of remifentanil to block the hemodynamic response to tracheal intubation was 3.7 ng/ml during inhalational induction with 1 MAC desflurane. (Korean J Anesthesiol 2011; 60: 12-18)

Key Words: Anesthesia, Desflurane, Inhalation, Intravenous, Remifentanil.

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Introduction

A high alveolar concentration of volatile anesthetic often depresses the pre-intubation blood pressure to clinically unacceptable levels in order to achieve normal blood pressure after tracheal intubation [1]. In case of desflurane, a rapid increase of the alveolar concentration greater than 1 minimum alveolar concentration (MAC), which was required to blunt the hemodynamic response to tracheal intubation, was frequently related with tachycardia and hypertension [2,3]. Suppression of the sympathetic responses to desflurane itself as well as to tracheal intubation required cumbersome pharmacologic interventions during the brief period of anesthesia induction [4].

Recent studies have indicated that low concentrations of volatile anesthetics were frequently combined with a large dose of opioid to ensure unawareness and hemodynamic stability during surgery [5,6]. The concept of balanced anesthesia may be adopted for anesthesia induction with desflurane [7]. We thought that an inspiratory desflurane concentration of 1 MAC would be sufficient to induce unawareness, resulting in less desflurane-related complications than that with higher concentrations of desflurane. Combining a target-controlled infusion (TCI) of remifentanil would suppress the signs of desflurane-related stimulation and provide anesthetic synergy with desflurane, hemodynamic stability and convenient control to maintain stable effect-site concentrations.

In the current study, our primary end-point was to determine a median effective effect-site concentration of remifentanil to block the hemodynamic response to tracheal intubation during the administration of an inspiratory desflurane concentration of 1 MAC, and we did this by performing an up-and-down study (a dose-finding study to investigate a dose with a certain probability of effectiveness, usually 50%, in sequentially allocated patients). In addition, the desflurane and remifentanil-related complications were assessed during the study.

Materials and Methods

After obtaining the approval of our institutional review board and written informed consent from the patients, the American Society of Anesthesiologists I-II patients (aged 18−60 years) who were scheduled for elective general surgeries such as breast and thyroid surgeries and laparoscopic cholecystectomy were consecutively enrolled into the study. The patients who were anticipated to have difficulty with laryngoscopy, those with a recent history of or those with ongoing cardiac, pulmonary or renal diseases and those currently taking analgesic or antihypertensive medications were excluded from the study. No patients received premedication before the study.

The patient arrived in the operating room with an 18 G intravenous catheter on the forearm, and standard monitoring was applied to the patient, including electrocardiography, noninvasive blood pressure and pulse oxymetry (Solaris 8000M Patient Monitor, GE Medical Systems, Milwaukee, WI). A bispectral index (BIS) monitor (BIS-XP monitor, Aspect Medical Systems Inc., Natick, MA) was applied to the patient. Remifentanil (Ultiva™ inj., 1mg vial, GlaxoSmithKline, Belgium) was diluted into 50 ml of normal saline (20 μg/ml solution) and this was put into a commercial TCI device (Orchestra® Base Primea, Fresenius Vial, France). A microvolume extension tube was connected to the intravenous catheter via a 3-way stopcock. The TCI device was operated in the effect-site control mode using the pharmacokinetic model of Minto and colleagues [8]. The end-tidal concentrations of desflurane and carbon dioxide were measured with a multi-gas analyzer integrated into the anesthetic ventilator (Primus, Dräger Medical AG & Co. KGaA, Germany).

The starting target effect-site concentration of remifentanil was empirically set at 5 ng/ml. Using this starting concentration, our preliminary study showed that the incremental or decremental change in the target concentration was as large as 20% of the initial concentration. We finally determined that the starting and step-size concentrations were 5 and 1 ng/ml, respectively. The response of each patient determined the target concentration of remifentanil administered to the next patient. A successful response was defined as the increase of heart rate (HR) or mean arterial pressure (MAP) at 1 min after intubation that did not exceed 20% of the value just before laryngoscopic intubation. If the HR or MAP exceeded 20% of the pre-intubation value, then it was defined as a failed response. If a successful response was noted, then the target concentration of remifentanil was lowered by 1 ng/ml for the next patient, and in case of a failure response, the target concentration of remifentanil was increased by 1 ng/ml. Before entering the test, rescue regimens to treat the adverse effects of remifentanil or desflurane were prepared as follows: atropine for bradycardia, ephedrine for hypotension, esmolol for tachycardia and both propofol and succinylcholine for chest rigidity and airway spasm.

The schematic of this study is outlined in Fig. 1. The patients received remifentanil via the effect-site TCI under oxygen supplement through a fitted facial mask. Remifentanil-associated major complications such as chest wall rigidity, bradycardia and hypotension were assessed until the predicted target effect-site concentration of remifentanil reached the preset level. Desflurane administration followed through the fitted facial mask along with 8 L/min of 100% oxygen. With 100% oxygen, the dial of the desflurane vaporizer was set at a 1 MAC concentration that was calculated using Mapleson's

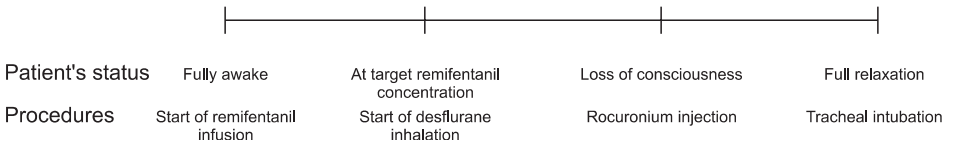

Fig. 1. Schematic representation of desflurane-remifentanil anesthesia induction.

equation ($MAC_{age} = MAC_{40} \times 10^{-0.00269(age-40)}$, where MAC_{age} is the age-corrected MAC value and MAC_{40} is 1 MAC for a 40 year old patient. For example, 1 MAC of desflurane was 6.6 vol% for a 40-year-old patient and 5.8 vol% for a 60-year-old patient [9]. Spontaneous mouth breathing was encouraged until patient failed to respond to verbal commands to breathe deeply and open their eyes. During this period, the signs of desflurane-associated airway irritation (cough, excessive salivation, laryngospasm and bronchospasm) and the signs of sympathetic stimulation (tachycardia and hypertension) were assessed. When the patient lost consciousness, which was again confirmed with an Observer's Assessment of Alertness/Sedation (OAA/S) score of 1 [10], rocuronium 0.9 mg/kg was injected to facilitate tracheal intubation. Controlled manual ventilation continued for an additional 5 min to the supposed equilibriums of both remifentanil and desflurane. Tracheal intubation was then performed using direct laryngoscopy. After tracheal intubation was secured, the lungs were mechanically ventilated using an individually adjusted ventilator setting (tidal volume = 8 ml/kg, frequency = 10/min) at 2 L/min of fresh gas flow with 50% oxygen in air along with a lowered target concentration of remifentanil set at 2 ng/ml during the next 5 min.

The measured variables during the study included the HR, MAP and SpO_2, the end tidal concentrations of carbon dioxide ($EtCO_2$) and desflurane (EtDES) and the BIS values. These variables were measured at different time points such as the time before anesthesia induction (baseline), the time when the target effect-site concentration was reached (tCe), the time of loss of consciousness (LOC), just before laryngoscopic intubation (BI) and every 1 min during the first 5 min after intubation (I + 1, I + 2, I + 3, I + 4 and I + 5).

On the first postoperative day, the patients were questioned about whether they had an explicit recall of memory about the events during induction.

Statistical analysis

When a success response was followed by a failure response, such a change in response was termed a "crossover". A crossover showed a midpoint concentration between consecutive success and failure response concentrations. This study was terminated after six crossovers had occurred. The six crossovers were averaged to determine a median effective effect-site concentration (EC_{50}) of remifentanil [11] (Fig. 2). The involved

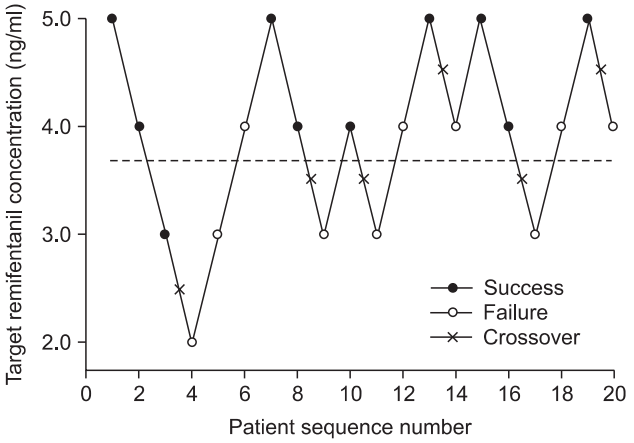

Fig. 2. Up-and-down sequence. A successful response was defined as the increase of the heart rate or mean arterial pressure at 1 min after intubation that did not exceed 20% of the value just before laryngoscopic intubation. If the heart rate or mean arterial pressure exceeded 20% of the pre-intubation value, then it was defined as a failed response. A change between consecutive successful and failed responses is a "crossover" with a midpoint concentration between the successful and failed concentrations. Six crossovers were averaged to determine a median effective effect-site concentration of remifentanil.

patients were divided into 2 groups such as success and failure groups according to the post-intubation responses. The group characteristics were compared using unpaired t-tests and Fisher's exact test. The complication rates were compared with the chi-square test. For the measured variables, a t-test was performed for comparison of two means, and repeated measures analysis of variance with the Student-Newman-Keuls post hoc test was used for comparing several means. A correlation test was done to reveal the relationship between the remifentanil concentrations and the time to LOC. The data is presented as means ± SDs. SPSS (version 12, SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. P values < 0.05 were considered significant.

Results

A total of 22 patients entered the study. Two patients were dropped during the study because of unpredicted difficult laryngoscopy (the 5th patient) and severe bradycardia (HR = 35 bpm) during tracheal intubation (the 13th patient); anesthesia induction was uneventful after 3 attempts of direct laryngoscopy

and an atropine injection, respectively. However, these two patients were excluded from the analysis, and the same target concentrations were tried again for the next patients. Finally, 20 patients were included in the analysis (Table 1). From 6 crossovers, the median effective effect-site concentration of remifentanil to blunt the hemodynamic responses to laryngoscopic tracheal intubation was calculated as 3.7 ng/ml (Fig. 2).

The success and failure groups included 10 patients each. The groups' characteristics were comparable between the two groups except for the target remifentanil concentrations (Table 1). The only difference of the measured variables between the two groups was that the increases of HR and MAP after tracheal intubation were significantly less in the success group, as indicated by the group definition.

Until the remifentanil concentration reached the preset level, all the patients were fully awake (OAA/S = 5). All the patients maintained self-respiration and followed verbal commands to breathe deeply during desflurane inhalation. The $EtCO_2$ was maintained in the lower normal range during remifentanil pretreatment and desflurane inhalation (34 ± 5 and 32 ± 5 mmHg, respectively). The exhaled concentration of desflurane was 0.7 ± 0.1 MAC at the time of LOC and 0.7−0.8 MAC thereafter. The BIS values were not different between baseline (96 ± 2) and the time when the target remifentanil concentration was achieved (92 ± 5). The BIS dropped slightly at the time of LOC (85 ± 4), yet a significant reduction was noted at the time of intubation (60 ± 14). The BIS was maintained between 46 and 53 during the next 5 min (Fig. 3). The mean time to LOC after desflurane inhalation was 125 ± 22 s. The time to LOC was not correlated with the combined remifentanil concentrations (R = −0.208, P = 0.379).

Any complications related with remifentanil TCI were not observed except for mild dizziness in three patients. A sign of airway irritation was noted in one patient, in whom mild and transient cough occurred during desflurane inhalation when 2 ng/ml of remifentanil was infused. Neither tachycardia nor hypertension occurred during desflurane inhalation. No hypoxic episode was noted during the study. None of the patients complained of discomfort during desflurane inhalation and none were associated with explicit recall of memory.

Discussion

In the current study, we demonstrated that inhalation of desflurane combined with remifentanil TCI resulted in uncomplicated anesthesia induction. Our up-and-down study showed that 3.7 ng/ml was the EC_{50} of the remifentanil effect-site concentration to attenuate the hemodynamic response to tracheal intubation when combined with 1 MAC desflurane.

Two frequent problems related with the use of desflurane are sympathetic stimulation and signs of airway irritation during anesthesia induction. Sympathetic hyperactivity in the form of hypertension and tachycardia was noted during increasing the desflurane concentration from 1.0 to 1.5 MAC in healthy young volunteers [2]. Increasing the alveolar concentration of desflurane from 0.55 MAC to 1.66 MAC caused doubling of the blood pressure and heart rate, and 10-fold increase of the plasma catecholamine level [3]. Anesthesia induction with desflurane was troublesome because of sudden rises of the HR and blood pressure during desflurane administration, and the overlapped tachycardia or hypertension after tracheal intubation could be detrimental to susceptible patients. Signs of airway irritation such as coughing, laryngospasm, breath-holding, copious secretions and excitatory movements also occurred when high concentrations of desflurane were administered [12]. The high pungency of desflurane mades volatile induction of anesthesia with desflurane unacceptable. However, these two complications were minimal or not evident when desflurane was administered at concentrations less than 1 MAC [13,14]. Thus, we postulated that the desflurane-related complications would be eliminated by using as low as 1 MAC of desflurane. The inspiratory concentration rather than expiratory

Table 1. Group Characteristics

Group	Total	Success	Failure
Number of patients	20	10	10
Gender (M/F)	2/18	0/10	2/8
Age (yr)	41 ± 9	42 ± 8	40 ± 10
Height (cm)	161 ± 7	162 ± 5	160 ± 9
Weight (kg)	61 ± 11	63 ± 10	59 ± 11
Time to unawareness (sec)*	125 ± 22	121 ± 17	129 ± 26
Target remifentanil concentration (ng/ml)	3.9 ± 0.9	4.4 ± 0.7	3.4 ± 0.7†
Complications	Cough (1)	None	Cough (1)

If an increase of the heart rate or mean arterial pressure was confined to 20% of the pre-intubation value following laryngoscopic intubation, then the patient wasincluded in the success group. If the heart rate or mean arterial pressure exceeded 20% of the pre-intubation value, then the patient was included in the failure group. *Elapsed time from the start of desflurane inhalation to patient's unawareness, †P = 0.014 vs. the success group.

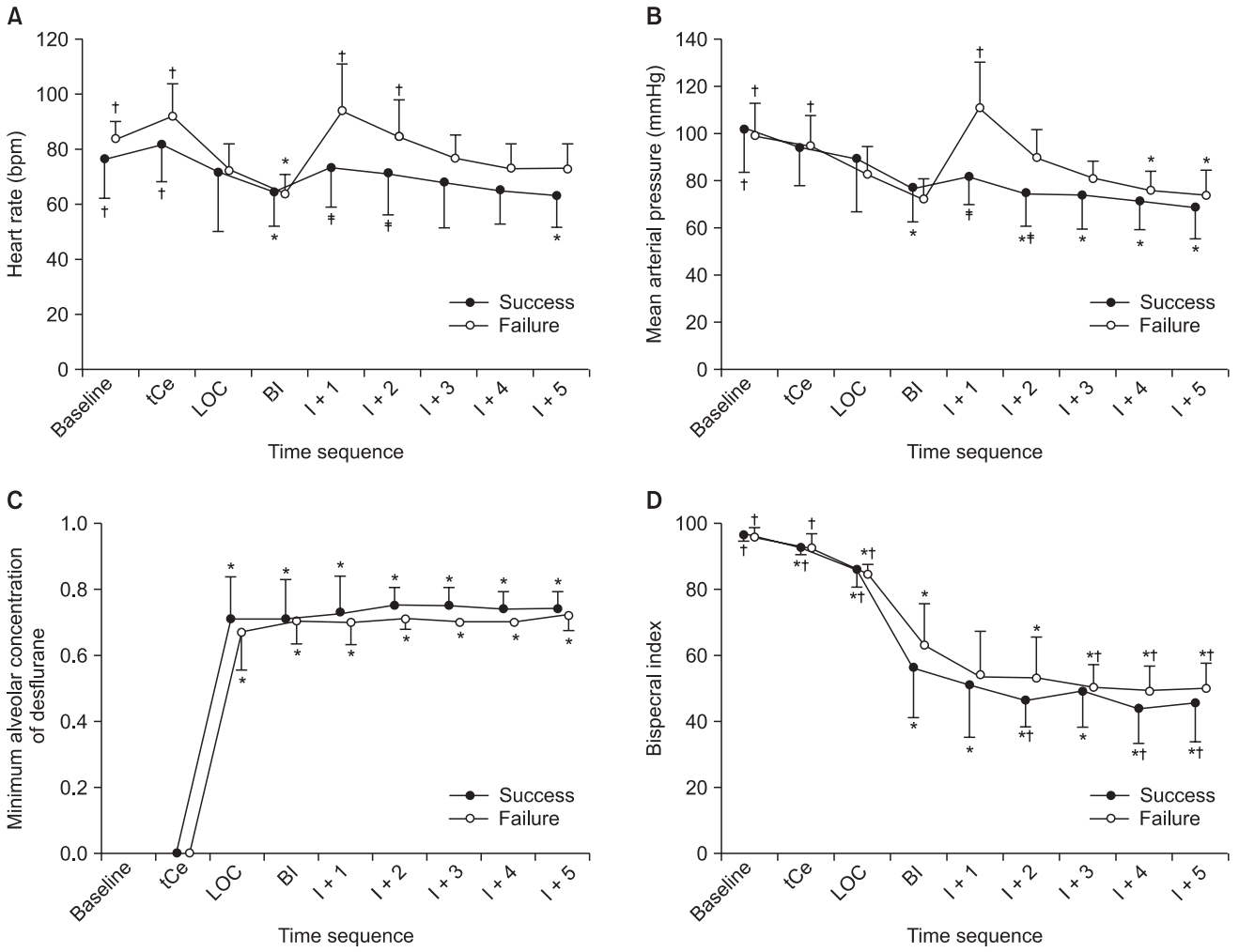

Fig. 3. Sequential comparison of the changes in the heart rate, mean arterial pressure, the minimum alveolar concentration and the bispectral index between the success and failure groups during the study. If an increase of the heart rate or mean arterial pressure was confined to 20% of the pre-intubation value following laryngoscopic intubation, then the patient was included in the success group. If the heart rate or mean arterial pressure exceeded 20% of the pre-intubation value, then the patient was included in the failure group. Baseline: the time before anesthesia induction, tCe: the time when the targeted effect-site concentration was reached, LOC: the time when the patient became unconscious, BI: just before laryngoscopic intubation, I + 1, I + 2, I + 3, I + 4 and I + 5: every 1 min during the first 5 min after intubation. *P < 0.05 vs. the baseline value, †P < 0.05 vs. the BI value, ‡P < 0.05 vs. the failure group.

concentration of desflurane would be set to 1 MAC because the airway receptors were the afferent site of sympathetic activation independent of the changes in the systemic anesthetic concentrations [15]. However, anesthesia induction with a low concentration of desflurane still requires an anesthetic adjuvant such as opioid in order to remove the residual desflurane complications and to get analgesic support during tracheal intubation.

Co-administration of fentanyl successfully attenuated the desflurane-related complications during desflurane anesthesia induction. Previous clinical studies have demonstrated that 1 and 1.5 μg/kg of intravenous fentanyl were effective to treat airway irritability and sympathetic hyperactivity following desflurane administration, respectively [4,16]. Larger doses such as 4 and 5−10 μg/kg of intravenous fentanyl blocked the hemodynamic response to tracheal intubation [17,18]. However, bolus fentanyl seems less practical because repetitive injections of different doses are required along with the time course of anesthesia induction. In the current study, we adopted the TCI of remifentanil to deliver a stable analgesic concentration on the basis of an integrated pharmacokinetic model and a computer-controlled infusion pump. Moreover, we targeted the highest level of stimulus such as an intubation response because desflurane-related complications are less intense responses than the hemodynamic response to tracheal intubation according to the above-mentioned dose-

response relationships. The safety of a pretreatment infusion at considerably high concentration was previously demonstrated by Lee and colleagues [19].

Using a low concentration of desflurane, one of our concerns was whether inhaling 1 MAC desflurane was sufficient to induce unawareness. The MAC-awake, which insures unawareness in 50% of the patients receiving the agent, was 0.36 MAC for desflurane [20]. Anesthetic concentrations 1.5−2 times the MAC-awake were related with suppression of recall of memory and preclusion of awareness in 100% of patients [21]. Nel and colleagues [22] determined the time to achieve an expired concentration to an inspired concentration ratio of 0.7 was 2 min during the initial administration of desflurane using high flow fresh gas. Our result showed that twice the MAC-awake (0.7 MAC) end-tidal desflurane was achieved in 2 min by inhaling 1 MAC of desflurane. At this concentration, all the patients lost their consciousness and none of them complained of recall of memory postoperatively. However, the shortening of the LOC time in the patients who received more remifentanil, according to the opioid-volatile synergy on hypnosis [23], was not revealed in this study. This might be due to the weak influence of the combined opioid on hypnosis with a ceiling effect at lower concentrations [17,24]. The small sample size of this up-and-down study might also have been responsible for this. Nonetheless, this balanced induction technique may be acceptable from a viewpoint of the rapidity. The time to LOC was not prolonged compared with the induction times using the TCI of propofol (100 s) or inhalational induction with sevoflurane (41−178 s) or the previous studies that tried volatile induction with desflurane-nitrous oxide at higher MAC equivalents (2−4 min) [16,25-27].

This study might be criticized for several points. First, performing volatile induction with desflurane may be criticized when patients have intravenous routes. There is consensus for the use of volatile induction for cases with failed intravenous catheterization, and especially in children. In the current study, volatile induction was considered from the beginning to eliminate the effect of confounding factors such as using an intravenous hypnotic agent. However, volatile induction balanced with opioid assured stable vital signs since an abrupt increase of anesthetic concentrations by either an overpressurized volatile agent or a bolus of intravenous anesthetic was avoided [28]. Eliminating the pain of propofol injections was also advantageous. We do not claim that this method has priority over the intravenous induction technique, yet the advantages of inhalational induction should be considered. Second, the desflurane requirement might be further reduced. Billard and colleagues noted that optimal balance was achieved at the MAC-awake concentration of desflurane when this was combined with intermediate concentrations of remifentanil, such as 5−7 ng/ml effect-site concentrations of remifentanil [24]. However, a response surface model of opioid-volatile synergy suggested that at least a 1.3 vol% (0.7 MAC) of sevoflurane was required to assure a 95% possibility of hypnosis in the absence of adjuvant remifentanil [21]. Concerns about intraoperative awareness and postoperative recall made it crucial to maintain a 0.7 MAC of end-tidal desflurane because the combined remifentanil concentration might be lowered to 0 ng/ml during the up-and-down sequence. Finally, this study just aimed at finding a median effective concentration of remifentanil. Anesthetic practices frequently require the EC_{95} values, yet the conventional up-and-down sequence failed to get such value because of the limited study design [29]. Furthermore, the efficacy and safety of the calculated EC_{95} value is not guaranteed because the value exceeded the tested range in the current study. A future study may be required to validate the EC_{95} value.

In conclusion, this up-and-down study revealed that 3.7 ng/ml was a median effective effect-site concentration of remifentanil to suppress tachycardia and hypertension following laryngoscopic tracheal intubation when combined with 1 MAC of desflurane. Hemodynamic stability and the absence of complication during anesthesia induction proved that this balanced technique was a feasible option for anesthesia induction with desflurane. We suggest a simple technique such as administering desflurane and remifentanil at fixed concentrations such as 1 MAC and 3.7 ng/ml, respectively, during the entire induction period.

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