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Effect-site concentration of remifentanil for smooth inhalational induction with desflurane

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Abstract

Objective: To determine the effect-site concentration (Ce) of remifentanil target-controlled infusion required for a smooth inhalational induction without airway irritation using desflurane in a stepwise incremental manner for 50% of patients (EC_{50}) and 95% of patients (EC_{95}).

Methods: Patients with an American Society of Anesthesiologists physical status I and II, aged 19–60 years undergoing elective surgery were enrolled in this study. When target Ce of remifentanil was reached, desflurane was inhaled at 4 vol% initially and then it was increased to 8 and 12 vol% at intervals of 30 s. Smooth induction was regarded as an absence of airway irritation signs and excitatory movements. The EC_{50} and EC_{95} values for remifentanil were determined using a modified Dixon's up-and-down method as well as an isotonic regression method with a bootstrapping approach.

Results: The EC_{50} and EC_{95} of remifentanil for smooth induction during inhalation of desflurane were 3.40 ng/ml (95% confidence interval [CI] 2.42, 4.38 ng/ml) and 4.31 ng/ml (95% CI 2.15, 5.98 ng/ml), respectively.

Conclusion: Prior administration of remifentanil could provide smooth inhalational induction with desflurane in a stepwise increment.

Keywords

Anaesthetic techniques, induction, desflurane, remifentanil, target-controlled infusion

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Introduction

Desflurane has the lowest blood–gas partition coefficient among all inhalation anaesthetics.[1] Therefore, it has been predicted that desflurane is suitable for rapid induction and recovery from general anaesthesia.[2,3] However, the pungent nature of desflurane

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limits its use in inhalation induction because it can cause a high incidence of airway irritation, including breath holding, coughing, excessive secretion, laryngospasm, and excitatory movements.[4,5]

Opioids are effective in reducing the airway irritation caused by desflurane.[4–7] Preadministration of an opioid before desflurane has been reported to be able to make the transition from being awake to loss of consciousness (LOC) smooth and feasible without causing airway irritation.[4,5,8,9] Remifentanil is an ultrashort-acting opioid; the onset time is very rapid and the context sensitive half-life is 3–5 min.[10,11] Therefore, it is easy to titrate and adjust remifentanil to obtain its optimal dose without the concern of delayed recovery. Two studies have reported airway irritation-free results following the administration of remifentanil prior to desflurane being used for inhalation induction.[8,9] The desflurane used in these previous studies was limited to 1 minimum alveolar concentration (MAC) of the dial of the vapourizer,[8,9] implying that the expiratory concentration was lower than 1 MAC, which means the actual concentration of desflurane was lower than 1.0–1.5 MAC, the threshold for airway irritation.[12,13] Therefore, the previous airway irritation-free results could be due to the low MAC of desflurane used in these studies,[8,9] regardless of the prior administration of remifentanil. In addition, the use of a low MAC of desflurane cannot guarantee the loss of consciousness under the potent stimuli of intubation. Therefore, we hypothesized that the effect of remifentanil on airway irritation could work on desflurane induction in a stepwise incremental manner using a higher concentration of desflurane, which is more common for inhaled induction to ensure that LOC is achieved in patients. The objective of this study was to determine the effect-site concentration of remifentanil target-controlled infusion required for a smooth inhalational induction without airway irritation using desflurane in a stepwise incremental manner for 50% of patients (EC_{50}) and 95% of patients (EC_{95}).

Patients and methods

Patient population and study design

This prospective observational study enrolled consecutive patients who met the following criteria at the Department of Anaesthesiology and Pain Medicine, Ajou University Hospital, Suwon, Republic of Korea between January 2015 and August 2015. The inclusion criteria were as follows: (i) American Society of Anesthesiologists physical status I and II;[14] (ii) aged 19–60 years; (iii) patients who were undergoing elective surgery under general anaesthesia. The exclusion criteria were as follows: (i) suspected difficult airway; (ii) known history of reactive airway disease. The study protocol was approved by the Institutional Review Board (no. AJIRB-MED-CT4-14-327) of Ajou University Hospital, Suwon, Republic of Korea. It was registered at ClinicalTrials.gov (NCT 02379715) and written informed consent was obtained from all patients.

Anaesthesia induction methods

Venous access was obtained from all patients using a 20 G intravenous catheter inserted into the forearm whilst the patient was on the ward. Patients received no premedication. Pulse oximetry, electrocardiography, and noninvasive blood pressure were performed for patients after they arrived at the operating room. Remifentanil (40 μg/ml solution) was loaded into a target-controlled infusion device (Orchestra® Base Primea; Fresenius Vial, Brézins, France) using the pharmacokinetic model of Minto et al.[15] Inspiratory and expiratory concentrations of desflurane were measured using a gas analyser within an anaesthesia ventilator (Dräger Primus®; Drägerwerk, Lübeck, Germany).

After patients were preoxygenated with 100% oxygen at 4 l/min using a face mask for 3 min, infusion of remifentanil was commenced. If the respiratory rate was <8 breaths/min, the patient was encouraged to breath. Their chest wall rigidity (chest tightness and difficulty in breathing) accompanied by desaturation (< 95%) was assessed for active management. When the target effect-site concentration of remifentanil was reached, the vapourizer of desflurane was dialled at 4 vol% initially. The concentration of desflurane was then increased to 8 and 12 vol% at intervals of 30 s. The concentration of desflurane was also calculated as a MAC value. The MAC value was the age-corrected MAC value of each patient calculated by Mapleson's method.[16] Each patient was asked to open his or her eyes every 10 s during inhalation of desflurane. The time when the patient did not respond to this command was regarded as being when the patient had achieved LOC. After LOC was achieved, 0.6 mg/kg rocuronium was administered via intravenous (i.v.) injection. Tracheal intubation was then performed 90 s after the administration of 0.6 mg/kg rocuronium i.v. If airway irritation signs, such as breath holding, coughing, laryngospasm and excitatory movements (head movement, limb movement, verbal/forceful removal of the mask by the patient), developed during the induction period, the dial of the vapourizer of desflurane was then set to zero. In addition, 4 mg/kg thiopental i.v. and 0.6 mg/kg rocuronium i.v. were administered immediately. After that, intubation and routine anaesthesia were continued. Breath holding was considered no breathing movements for > 30 s. Laryngospasm was defined as complete airway obstruction associated with decrease in oxygen saturation for > 20 s. Regardless of the severity of the airway irritation sign, the presence of irritability was considered as a failed state and the onset time of airway irritation signs, inspiratory and end-tidal concentrations of desflurane were recorded.

The LOC time was defined as the time from the start of desflurane inhalation via a face mask to the point that the patient did not respond to the verbal command. The LOC time, inspiratory and end-tidal concentrations of desflurane at the LOC point were recorded. Haemodynamic data were recorded at baseline (T0), when the target effect-site concentration of remifentanil was reached (T1), 1 min after desflurane inhalation (T2), and at LOC (T3). In the case of bradycardia (heart rate < 45 beats/minute [bpm]) or tachycardia (heart rate > 130 bpm), 0.5 mg atropine i.v. or 0.2 mg/kg esmolol i.v. were administered, respectively. Hypertension and hypotension were treated at the discretion of the attending anaesthesiologists (J.Y.Y., Y.J.C., and S.Y.L.). The investigators (H.W.J. and H.B.P.) who conducted the inhaled induction of desflurane and assessed the complications and airway irritation were blinded to the effect-site concentration of remifentanil.

The effect-site concentration of remifentanil for preventing airway reactivity was determined using a modified Dixon's up-and-down method.[17,18] The initial effect-site concentration of remifentanil was 4 ng/ml. The next target effect-site concentration of remifentanil was determined based on the response of the previous patient. A successful response was regarded as the absence of breath holding, coughing, laryngospasm, or excitatory movements. If any of these symptoms occurred, it was regarded as a failure and the next target effect-site concentration of remifentanil was increased by 0.5 ng/ml. Conversely, if the desflurane induction was successful, the next target effect-site concentration of remifentanil was decreased by 0.5 ng/ml.

Statistical analyses

The patients were enrolled in this study until eight crossover pairs were obtained according to Dixon's sequential allocation method.[18]

The sample size was decided based on prior literature that demonstrated that the modified Dixon's up-and-down method required more than the minimum six crossover points to minimize the inaccuracy of the individual study.[19] Thus, data from eight independent crossovers of patients were collected for this study. The EC_{50} of remifentanil was defined as the mean value of independent crossover pairs (i.e. failure to success of smooth induction). The R statistical software package version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) was used for calculations using the isotonic regression method to estimate EC_{50} and EC_{95} along with 95% confidence interval (CI). The CI was estimated using the bootstrapping approach.[20] Other statistical analyses were performed using the SPSS® statistical package, version 11.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Comparisons between the success and failure groups were analysed using independent *t*-test, χ^2-test, Fisher's exact test, or Mann–Whitney *U*-test where appropriate. Haemodynamic data were analysed with repeated measures of analysis of variance, followed by paired *t*-test for comparisons across successive time-points. Data were reported as mean ± SD or the *n* of patients. A P-value < 0.05 was considered statistically significant.

Results

This study enrolled 26 patients (12 males, 14 females) and the demographic characteristics of the success ($n = 14$) and failure ($n = 12$) groups are summarized in Table 1. There were no significant differences between the two groups. The anaesthesia induction characteristics for the two groups are shown in Table 2. A respiratory rate < 8 breaths/min was observed in four patients in each group and they responded to verbal commands to breath. Chest wall rigidity accompanied by desaturation (< 95%) did not occur. Airway irritation signs in the failure group included excitatory movements in all patients (12/12; 100%). Cough presented in five patients (42%), breath holding presented in two patients (17%) and laryngospasm did not occur in any patient. The mean ± SD onset time of airway irritation signs was recorded in the failure group instead of LOC time (169.0 ± 23.9 s). The mean ± SD inspiratory and expiratory concentrations of desflurane at the onset of airway irritation signs were 8.5 ± 1.3 vol% (1.31 ± 0.21 MAC) and 6.6 ± 0.9 vol% (1.01 ± 0.13 MAC), respectively. The mean ± SD LOC time in the success group was 167.6 ± 61.0 s. The mean ± SD inspiratory and expiratory concentrations of desflurane were 8.2 ± 1.7 vol% (1.33 ± 0.27 MAC) and 5.8 ± 1.0 vol% (0.95 ± 0.19 MAC), respectively.

Individual data of concentration-response within the up-and-down sequences are shown in Figure 1. The mean ± SD EC_{50} of remifentanil for smooth induction without airway irritations during inhalation of desflurane via a modified Dixon's up-and-down method

Table 1. Demographic characteristics of patients undergoing elective surgery under general anaesthesia who participated in this study to examine the effect-site concentration of remifentanil target-controlled infusion required for a smooth inhalational induction without airway irritation using desflurane.

	Success group $n = 14$	Failure group $n = 12$
Sex, male/female	6/8	6/6
Age, years	43.4 ± 8.5	46.8 ± 10.5
Weight, kg	66.1 ± 10.9	62.2 ± 11.2
Height, cm	167.3 ± 6.7	165.9 ± 8.9
ASA physical status, I/II	13/1	11/1

Values are expressed as mean ± SD or *n* of patients.
ASA, American Society of Anesthesiologists.
No significant between-group differences ($P \geq 0.05$); independent *t*-test, χ^2-test, or Fisher's exact test.

Table 2. Anaesthesia induction characteristics of patients undergoing elective surgery under general anaesthesia who participated in this study to examine the effect-site concentration of remifentanil target-controlled infusion required for a smooth inhalational induction without airway irritation using desflurane.

	Success group $n = 14$	Failure group $n = 12$
Remifentanil Ce, ng/ml	3.7 ± 0.6	3.2 ± 0.6*
Airway irritation		
Cough	0	5 (42%)*
Breath holding	0	2 (17%)
Laryngospasm	0	0 (0%)
Excitatory movement	0	12 (100%)*
Onset time, s	–	169.0 ± 23.9
Desflurane concentration at the onset of airway irritation	–	
Des.in, vol% (MAC)	–	8.5 ± 1.3 (1.31 ± 0.21)
Des.ex, vol% (MAC)	–	6.6 ± 0.9 (1.01 ± 0.13)
LOC time, s	167.6 ± 61.0	–
Desflurane concentration at LOC		
Des.in, vol% (MAC)	8.2 ± 1.7 (1.33 ± 0.27)	–
Des.ex, vol% (MAC)	5.8 ± 1.0 (0.95 ± 0.19)	–

Values are expressed as mean ± SD or *n* of patients (%).
Ce, concentration at effect-site; Des.in, inspiratory concentration of desflurane; Des.ex, expiratory concentration of desflurane; LOC, loss of consciousness.
*$P < 0.05$ compared with the success group; independent *t*-test or Fisher's exact test.

was 3.56 ± 0.70 ng/ml. The EC_{50} and EC_{95} of remifentanil estimated by the isotonic regression method and the bootstrapping approach were 3.40 ng/ml (95% CI 2.42, 4.38 ng/ml) and 4.31 ng/ml (95% CI 2.15, 5.98 ng/ml), respectively (Figure 2).

Haemodynamic data are shown in Table 3. There were no significant differences between the two groups. There was no case of severe hypertension or tachycardia. One patient at T2 in the failure group and another patient at T3 in the success group was administered atropine to treat bradycardia. Their effect-site concentrations of remifentanil were both 4 ng/ml.

Discussion

The mean ± SD effect-site concentration of remifentanil (EC_{50}) for smooth inhalational induction with desflurane via a modified Dixon's up-and-down method was at 3.56 ± 0.70 ng/ml. The EC_{50} and EC_{95} of remifentanil estimated by the isotonic regression method were 3.40 ng/ml (95% CI 2.42, 4.38 ng/ml) and 4.31 ng/ml (95% CI, 2.15–5.98 ng/ml), respectively.

The high pungency of desflurane causes sympathetic stimulation and airway irritation during induction.[21,22] Opioids are expected to be an effective adjuvant during inhaled induction of desflurane because they can prevent the drawbacks of both cardiovascular stimulation[23,24] and airway irritation.[4–7] The current study mainly focused on airway irritation-free smooth transition from being awake to LOC during the inhalation of desflurane without using other intravenous anaesthetics. To date, two studies have reported smooth induction by using preadministration of remifentanil and inhalation of desflurane.[8,9] As described

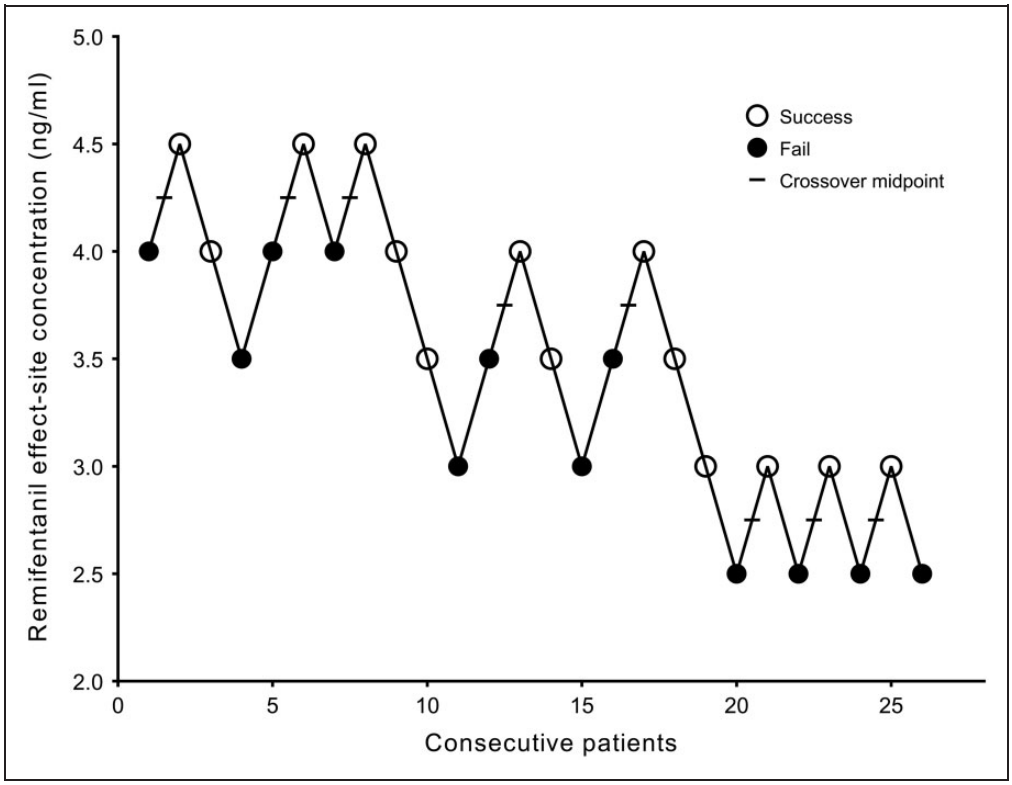

Figure 1. Consecutive successful or failed smooth induction over predetermined concentrations of remifentanil with desflurane inhalation (initial predetermined concentration of remifentanil was 4.0 ng/ml for the first patient). Eight pairs of failure–success sequences were received for analysis with the modified Dixon's up-and-down method. The mean ± SD effect-site concentration of remifentanil for smooth induction with desflurane in 50% of patients was 3.56 ± 0.70 ng/ml.

earlier, the concentration of desflurane used in these previous two studies was limited to around 1 MAC of the dial of the vapourizer.[8,9] The exhaled concentration measured in one report was around 0.7 MAC,[9] which is not enough to cause airway irritation because the threshold of desflurane for irritating the airway is known to be 1.0–1.5 MAC.[12,13] Therefore, these previous airway irritation-free results could be due to a low concentration of desflurane regardless of the use of remifentanil. The use of a low concentration of desflurane may not ensure LOC in all patients with the potent stimuli of intubation, although the authors reported successful induction of anaesthesia.[9] In addition, the optimal dose of remifentanil was chosen to blunt the haemodynamic response to intubation, unlike the current study.[9] This present study chose a stepwise incremental manner using a high concentration of desflurane because it would ensure LOC was achieved. Opioids can increase the threshold of airway irritation.[6] These present results revealed that remifentanil made smooth inhalation induction possible when using a high concentration of desflurane. This could make induction of anaesthesia using inhaled desflurane a feasible option in the clinical situation. With regard to cardiovascular stimulation, no severe hypertension or tachycardia was observed in the present study.

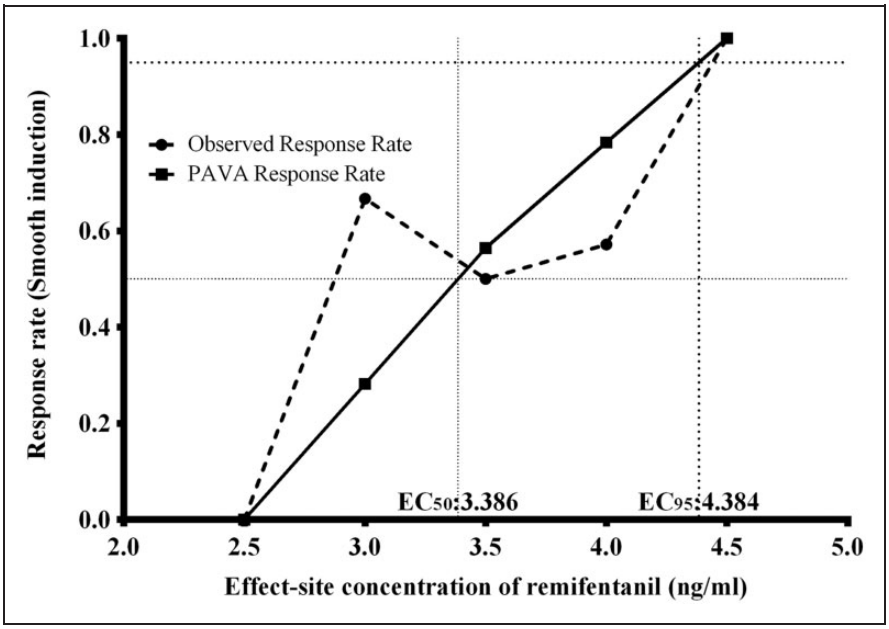

Figure 2. Observed and pooled adjacent violators algorithm (PAVA) response rate. The EC_{50} of remifentanil was 3.40 ng/ml (95% confidence interval [CI] 2.42, 4.38 ng/ml). The EC_{95} of remifentanil was 4.31 ng/ml (95% CI 2.15, 5.98 ng/ml). EC_{50}, effect-site concentration of remifentanil for smooth inhalational induction with desflurane in 50% of patients; EC_{95}, effect-site concentration of remifentanil for smooth inhalational induction with desflurane in 95% of patients.

Table 3. Mean arterial pressure and heart rate during inhalational induction of patients undergoing elective surgery under general anaesthesia who participated in this study to examine the effect-site concentration of remifentanil target-controlled infusion required for a smooth inhalational induction without airway irritation using desflurane.

	Success group $n = 14$	Failure group $n = 12$
Mean arterial pressure, mmHg		
T0	92.6 ± 7.7	93.7 ± 6.8
T1	91.3 ± 8.5	91.9 ± 9.1
T2	88.4 ± 10.5	93.4 ± 11.0
T3	85.7 ± 11.8*	90.3 ± 13.3
Heart rate, beats/min		
T0	73.4 ± 15.1	73.1 ± 15.5
T1	68.3 ± 12.4*	72.3 ± 15.2
T2	62.6 ± 13.1*	68.0 ± 16.2
T3	57.4 ± 12.9*	62.5 ± 9.3*

Values are expressed in mean $\pm$ SD.

T0, baseline; T1, when the target effect-site concentration of remifentanil was reached; T2, 1 min after desflurane inhalation; T3, at the loss of consciousness.

*$P < 0.05$ compared with baseline value T0; paired *t*-test.

No significant between-group differences ($P \geq 0.05$); repeated measures analysis of variance.

One previous study reported that 4 ng/ml remifentanil was able to minimize the haemodynamic change caused by inhalation induction using 1.7 MAC desflurane.[25] Thus, the effect-site concentrations of remifentanil observed in the current study of 3.7 ng/ml and 3.2 ng/ml in the success and failure groups, respectively, seemed to be able to prevent cardiovascular stimulation. However, when 4.31 ng/ml (EC_{95}) of remifentanil was used for smooth induction, caution was needed for haemodynamic stability.

The inspiratory and expiratory concentrations of desflurane at LOC in the success group of the current study were 8.2 vol% (1.33 MAC) and 5.8 vol% (0.95 MAC), respectively. It has been reported that the inspiratory and expiratory concentrations at LOC using desflurane alone or with nitrous oxide were 14.1–14.9 vol% and 10.1–10.9 vol%, respectively.[26,27] In a study using pretreatment with fentanyl and midazolam, the inspiratory and expiratory concentrations at LOC were 8.9 vol% and 5.3 vol%, respectively.[27] These results suggest that an opioid can decrease the anaesthetic requirement for LOC. The mean ± SD time to LOC was 167.6 ± 61.0 s in this present study. However, the lack of control group means that it is not possible to determine if this time was reduced by the use of an opioid. Whether or not pretreatment with an opioid shortens the LOC time remains controversial because one controlled study found a reduction,[5] whereas another study found no difference.[27] Considering that remifentanil produces dose-dependent respiratory depression, there is still a possibility that these respiratory depression effects offset to some extent the expected shortening effect of induction time due to a decrease of MAC of desflurane.

The main airway irritation sign was excitatory movements in the current study, which was in line with previous studies.[27,28] Excitatory movements occurred in all patients in the failure group. Cough was concurrently found in five of 12 (42%) patients and breath holding was found in two of 12 (17%) patients. There was no evidence of laryngospasm. Excitatory movements included verbal or forceful removal of the mask by the patient, plus head and limb movements. These excitatory movements could have been the result of the patient's response to the pungent stimuli or the expression of an excitatory stage (stage 2) of anaesthesia. Whatever the cause of the excitatory movements, their presence limited the anaesthesiologist's ability to increase the concentration of desflurane and they were the most common obstacle to the patient tolerating inhaled induction with desflurane.

The current study had several limitations. First, the same concentration of desflurane was used for patients of all ages, but the iso-MACs are somewhat different in patients aged 19 to 60 years.[28] Secondly, there was a basic bias between real plasma concentration and the calculated one for remifentanil based on the pharmacokinetic model of Minto et al.[15,29] Thirdly, the feasibility of inhaled induction of desflurane was based on the objective signs during inhalation. There might be dissatisfaction of patients despite the fact that they seemed to be calm during inhalation. This was not checked in this present study. Fourth, Dixon's up-and-down method has potential limitations for estimating EC_{95}. To overcome this limitation, this present study adopted the isotonic regression method and the bootstrapping approach as supplementary analyses for reducing bias and getting greater precision rather than using conventional methods.[20,30]

In conclusion, the EC_{50} and EC_{95} of effect-site concentrations of remifentanil required for smooth inhalational induction without airway irritation when using desflurane in a stepwise increment were 3.40 ng/ml and 4.31 ng/ml, respectively. Therefore, prior administration of remifentanil could provide smooth inhalational induction with desflurane.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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References

1. Kapoor MC and Vakamudi M. Desflurane - revisited. *J Anaesthesiol Clin Pharmacol* 2012; 28: 92–100.
2. Garry B, Torelli G and Yarnell R. Desflurane can be used to achieve smooth and rapid induction of anesthesia. *Anesthesiology* 1995; 82: 313–314.
3. Barter LS, Ilkiw JE, Pypendop BH, et al. Evaluation of the induction and recovery characteristics of anesthesia with desflurane in cats. *Am J Vet Res* 2004; 65: 748–751.
4. Kong CF, Chew ST and Ip-Yam PC. Intravenous opioids reduce airway irritation during induction of anaesthesia with desflurane in adults. *Br J Anaesth* 2000; 85: 364–367.
5. Lee C and Shim KS. The effects of intravenous lidocaine and alfentanil on airway irritability and hemodynamic stability during inhaled induction with desflurane: a randomized double-blinded studdy. *Korean J Anesthesiol* 2005; 49: 461–465.
6. Lee J, Oh Y, Kim C, et al. Fentanyl reduces desflurane-induced airway irritability following thiopental administration in children. *Acta Anaesthesiol Scand* 2006; 50: 1161–1164.
7. Galante D, Meola S, Milillo R, et al. Remifentanil infusion reduces desflurane airway irritation via proseal laryngeal mask in children. *Paediatr Anaesth* 2010; 20: 963–964.
8. Muchada R. Remifentanil+desflurane for inhalational induction without airway irritation and rapid post-anaesthetic recovery. Preliminary results in 100 patients. In: Gullo A (ed.) *Anaesthesia, pain, intensive care and emergency medicine — APICE*. Milan: Springer, 2004, pp.749–757.
9. Lee J and Jung CW. The target concentration of remifentanil to suppress the hemodynamic response to endotracheal intubation during inhalational induction with desflurane. *Korean J Anesthesiol* 2011; 60: 12–18.
10. Egan TD. Remifentanil pharmacokinetics and pharmacodynamics. A preliminary appraisal. *Clin Pharmacokinet* 1995; 29: 80–94.
11. Glass PS, Gan TJ and Howell S. A review of the pharmacokinetics and pharmacodynamics of remifentanil. *Anesth Analg* 1999; 89: S7–S14.
12. Jones RM, Cashman JN and Mant TG. Clinical impressions and cardiorespiratory effects of a new fluorinated inhalation anaesthetic, desflurane (I-653), in volunteers. *Br J Anaesth* 1990; 64: 11–15.
13. Arain SR, Shankar H and Ebert TJ. Desflurane enhances reactivity during the use of the laryngeal mask airway. *Anesthesiology* 2005; 103: 495–499.
14. American Society of Anesthesiologists. ASA Physical Status Classification System. https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system (approved 15 Oct 2014, assessed 25 May 2016).
15. Minto CF, Schnider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology* 1997; 86: 10–23.
16. Mapleson WW. Effect of age on MAC in humans: a meta-analysis. *Br J Anaesth* 1996; 76: 179–185.
17. Dixon WJ. The up-and-down method for small samples. *Journal of the American Statistical Association* 1965; 60: 967–978.
18. Dixon WJ. Staircase bioassay: the up-and-down method. *Neurosci Biobehav Rev* 1991; 15: 47–50.
19. Paul M and Fisher DM. Are estimates of MAC reliable? *Anesthesiology* 2001; 95: 1362–1370.
20. Pace NL and Stylianou MP. Advances in and limitations of up-and-down methodology: a precis of clinical use, study design, and dose estimation in anesthesia research. *Anesthesiology* 2007; 107: 144–152.
21. TerRiet MF, DeSouza GJ, Jacobs JS, et al. Which is most pungent: isoflurane, sevoflurane or desflurane? *Br J Anaesth* 2000; 85: 305–307.

22. Ebert TJ and Muzi M. Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers. A comparison with isoflurane. *Anesthesiology* 1993; 79: 444–453.
23. Yonker-Sell AE, Muzi M, Hope WG, et al. Alfentanil modifies the neurocirculatory responses to desflurane. *Anesth Analg* 1996; 82: 162–166.
24. Weiskopf RB, Eger EI 2nd, Noorani M, et al. Fentanyl, esmolol, and clonidine blunt the transient cardiovascular stimulation induced by desflurane in humans. *Anesthesiology* 1994; 81: 1350–1355.
25. Jeong HJ, Baik HJ, Kim JH, et al. Effect-site concentration of remifentanil for minimizing cardiovascular changes by inhalation of desflurane. *Yonsei Med J* 2013; 54: 739–746.
26. Kelly RE, Hartman GS, Embree PB, et al. A51 induction of anesthesia with desflurane: A comparison of conventional (C) and vital capacity rapid inhalation induction (VCRII) techniques. *Anesthesiology* 1990; 73: A51.
27. Kelly RE, Hartman GS, Embree PB, et al. Inhaled induction and emergence from desflurane anesthesia in the ambulatory surgical patient: the effect of premedication. *Anesth Analg* 1993; 77: 540–543.
28. Nickalls RW and Mapleson WW. Age-related iso-MAC charts for isoflurane, sevoflurane and desflurane in man. *Br J Anaesth* 2003; 91: 170–174.
29. Mertens MJ, Engbers FH, Burm AG, et al. Predictive performance of computer-controlled infusion of remifentanil during propofol/remifentanil anaesthesia. *Br J Anaesth* 2003; 90: 132–141.
30. Stylianou M and Flournoy N. Dose finding using the biased coin up-and-down design and isotonic regression. *Biometrics* 2002; 58: 171–177.