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Effect-site concentration of remifentanil required to blunt haemodynamic responses during tracheal intubation: A randomized comparison between single- and double-lumen tubes

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Abstract

Objective: To investigate the effect-site concentration of remifentanil required to blunt haemodynamic responses during tracheal intubation with a single-lumen tube (SLT) or a double-lumen tube (DLT).

Methods: Patients scheduled for thoracic surgery requiring one-lung ventilation were randomly allocated to either the SLT or DLT group. All patients received a target-controlled infusion of propofol and a predetermined concentration of remifentanil. Haemodynamic parameters during intubation were recorded. The effect-site concentration of remifentanil was determined using a delayed up-and-down sequential allocation method.

Results: A total of 92 patients were enrolled in the study. The effective effect-site concentrations of remifentanil required to blunt haemodynamic responses in 50% of patients (EC_{50}) estimated by isotonic regression with bootstrapping was higher in the DLT than the SLT group (8.5 ng/ml [95% confidence interval (CI) 8.0–9.5 ng/ml] versus 6.5 ng/ml [95% CI 5.6–6.7 ng/ml], respectively). Similarly, the effective effect-site concentrations of remifentanil in 95% of patients in the DLT group was higher than the SLT group (9.9 ng/ml [95% CI 9.8–10.0 ng/ml] versus 7.0 ng/ml [95% CI 6.9–7.0 ng/ml], respectively).

Conclusions: This study demonstrated that a DLT requires a 30% higher EC_{50} of remifentanil than does an SLT to blunt haemodynamic responses during tracheal intubation when combined with a target-controlled infusion of propofol.

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Keywords
Double-lumen tube placement, effect-site concentration, remifentanil

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Introduction

Tracheal intubation with direct laryngoscopy induces haemodynamic responses, including hypertension and tachycardia, which are mediated by increased sympathetic nervous system activity.[1] It is generally understood that intubation with a double-lumen tube (DLT) produces more intense haemodynamic responses than does intubation with a single-lumen tube (SLT).[2,3] This difference is believed to be the result of the larger external diameter of DLTs and associated carinal stimulation during DLT placement.

Remifentanil is a relatively new opioid with a rapid onset and short duration of effect, which makes it appropriate for the suppression of sympathetic responses induced by tracheal intubation.[4,5] The administration of remifentanil is suited for intravenous continuous infusion;[6] and target-controlled infusion (TCI) more effectively maintains haemodynamic stability than does continuous weight-adjusted infusion.[7] A previous study revealed the effective effect-site concentration of remifentanil that blunts haemodynamic responses in 50% of patients during SLT intubation.[5] However, the effect-site concentration of remifentanil that attenuates haemodynamic responses during DLT intubation remains unclear.

Based on the belief that DLT intubation induces more noxious stimuli and intense haemodynamic responses, we hypothesized that DLT intubation requires a higher effect-site concentration of remifentanil to maintain haemodynamic stability than does SLT intubation. The aim of this study was to determine and compare the effect-site concentration of remifentanil required to blunt haemodynamic responses during SLT and DLT intubation.

Patients & methods

Study population

This randomized study enrolled patients aged 20–65 years with an American Society of Anesthesiologists physical status of I to II who were scheduled for elective thoracic surgery requiring one-lung ventilation at Seoul National University Hospital, Seoul, South Korea between November 2011 and August 2012. The exclusion criteria were: (i) a body mass index of > 30 or $< 16\,kg/m^2$; (ii) cardiac, pulmonary, or renal disease; (iii) drug or alcohol abuse; (iv) current treatment with medications affecting the cardiovascular system or sympathetic nervous system; (v) a severely distorted anatomy of the tracheobronchial tree on chest radiographs. Eligible patients were randomly allocated to either the SLT or DLT group using a computer-generated random code by the sealed envelope method. The randomization sequence was generated by 1:1 allocation using a random block size of four by a statistician who was not involved in the study.

Ethical approval for this study (No. 1110-094-382) was provided by the Institutional Review Board of Seoul National University Hospital. The study complied with the Declaration of Helsinki and written informed consent was obtained from all patients. This study was registered at www.clinicaltrials.gov (NCT01542099).

Study procedures

Patients arrived in the operating room with an 18-gauge intravenous catheter in the forearm. Without premedication, the patients were monitored using non-invasive arterial blood pressure, pulse oximetry, and electrocardiography (Solar^{TM} 8000 M; GE Medical Systems Information Technologies, Milwaukee, WI, USA). The bispectral index (BIS) was also monitored (BIS VISTA^{TM}; Aspect Medical Systems Inc., Norwood, MA, USA). Anaesthesia was induced and maintained using propofol (Fresofol® 2%; Fresenius Kabi, Bad Homburg, Germany) and remifentanil (Ultiva®; GlaxoSmithKline, Rixensart, Belgium) using a TCI system (Orchestra® Base Primea; Fresenius Kabi). The TCI system was operated according to the Schneider model for propofol and the Minto model for remifentanil.[8,9] Remifentanil infusion was started with a predetermined target effect-site concentration, which is described below. Oxygen supplementation was also started through a tightly fitting face mask. After 1 min of remifentanil administration, propofol infusion was started with an effect-site concentration of 4 μg/ml to maintain a BIS of 40–50. This target concentration was chosen because an effect-site concentration of propofol of 3–4 μg/ml is common in clinical practice.[5,7,10] Deep breathing was encouraged until the patient failed to respond to verbal commands. After the patient lost consciousness, ventilation was assisted manually and 0.8 mg/kg rocuronium was administered intravenously to facilitate tracheal intubation. During controlled manual ventilation, radial artery cannulation was performed using a 20-gauge catheter for continuous blood pressure monitoring. The heart rate and mean arterial pressure were recorded just before intubation and at 1-min intervals for 5 min after intubation.

Five minutes after the rocuronium injection, tracheal intubation was performed using direct laryngoscopy. In the SLT group, a reinforced endotracheal tube with an 8.0-mm internal diameter (Mallinckrodt Medical Ltd., Athlone, Ireland) was placed such that the vocal cord was located between the black marks on the tube. Tracheal intubation was confirmed by capnography and auscultation. In the DLT group, only a left-sided DLT (Broncho-Cath®; Mallinckrodt Medical Ltd.) was used; the size of the DLT was selected according to the sex and height of the patient.[11] The depth of the DLT was predetermined according to a previous report.[12] After DLT intubation, the direction of the DLT was confirmed by auscultation. If tracheal intubation of the SLT or left-sided bronchial intubation of the DLT failed on the first attempt, the patient was withdrawn from the study and intubation was tried again using a different technique such as with a stylet or fibre optic bronchoscope. After collection of all study data, a bronchial blocker (Uniblocker; Fuji Systems Corp., Tokyo, Japan) was placed at the thoracotomy site in the SLT group for lung separation.

The effect-site concentration of remifentanil for each patient was determined by the haemodynamic response of the previously tested patients. The first patient in both the SLT and DLT groups received an effect-site concentration of remifentanil of 6 ng/ml. This starting dose was chosen according to a previous study demonstrating the effective effect-site concentration of remifentanil required to blunt the haemodynamic response in 50% of patients (EC_{50}) during SLT intubation.[5] If the haemodynamic response of the preceding patient was positive, the effect-site concentration was increased by 0.5 ng/ml for the subsequent patient. If the haemodynamic response was negative, the effect-site concentration for the subsequent patient was decreased by 0.5 ng/ml. The effect-site concentration of remifentanil remained constant during the data collection period. A positive haemodynamic

response was defined as a > 15% increase in mean arterial pressure or heart rate compared with the value just before intubation.[5] A negative haemodynamic response was defined as the absence of an increase in both heart rate and mean arterial pressure by > 15% compared with the value just before intubation. Haemodynamic monitoring and determination of the positive or negative haemodynamic responses were conducted by an independent anaesthesiologist who was not aware of the study purpose and blinded to the effect-site concentration of remifentanil. Patients with severe hypotension (mean arterial pressure < 50 mmHg) or bradycardia (heart rate < 40 beats/min) before intubation and those with failed intubation on the first attempt were withdrawn from the study, and the same effect-site concentration was repeated for the following patient.

Statistical analyses

Statistical analysis was performed using G*power 3.1.9.2 (Heinrich Heine Universität, Düsseldorf, Germany), SPSS® statistical package, version 18.0 (SPSS Inc., Chicago, IL, USA) for Windows®, and R 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria). The EC_{50} was defined as the effective effect-site concentration of remifentanil at which SLT or DLT intubation was performed without a haemodynamic response in 50% of patients. Likewise, the EC_{95} was defined as the effective effect-site concentration required to blunt the haemodynamic response in 95% of patients. The EC_{50} was analysed by the delayed up-and-down method,[13,14] in which the initial sequence of the same responses was truncated from the analysis to avoid bias from large first doses. The EC_{50} of remifentanil was determined by calculating the mean of the midpoint concentrations of all independent pairs of patients who manifested a crossover from a negative to a positive haemodynamic response. Data were also analysed by isotonic regression estimators and 9999 bootstrap replications to calculate the EC_{50} and EC_{95} along with the 95% confidence interval (CI).[15] The adjusted response probability was calculated by the pooled adjacent-violators algorithm.[14] A previous study[5] reported that the EC_{50} of remifentanil was 5 ng/ml during SLT intubation and the assumed standard deviation was 0.73 ng/ml. A sample size of 35 per group was calculated to detect a 0.5 ng/ml difference in the EC_{50} with a power 0.8 and $\alpha = 0.05$. The characteristics of the two groups and mean EC_{50} were compared using Student's *t*-test. Data are presented as mean ± SD. A value of $P < 0.05$ was considered statistically significant.

Results

In total, 92 patients were assessed for eligibility and randomly allocated to either the SLT or DLT group. Nine patients were excluded from the analysis because of two failed intubations on the first attempt in both groups: one right bronchial intubation in the DLT group and four low mean arterial pressures (<50 mmHg) during induction in the DLT group (Figure 1). The patient characteristics were similar between the two groups (Table 1). However, the tracheal intubation time was significantly longer in the DLT group than in the SLT group (33.4 ± 6.4 versus 25.1 ± 5.3 s, respectively; $P < 0.001$).

Figure 2 shows the up-and-down sequences for the haemodynamic response to SLT and DLT intubation. The mean EC_{50} of remifentanil required to blunt haemodynamic responses to SLT and DLT intubation were 6.3 ± 0.7 and 8.3 ± 0.7 ng/ml, respectively. The EC_{50} in the DLT group was significantly higher than in the SLT group ($P < 0.001$).

The EC_{50} of remifentanil required to blunt the sympathetic response as estimated

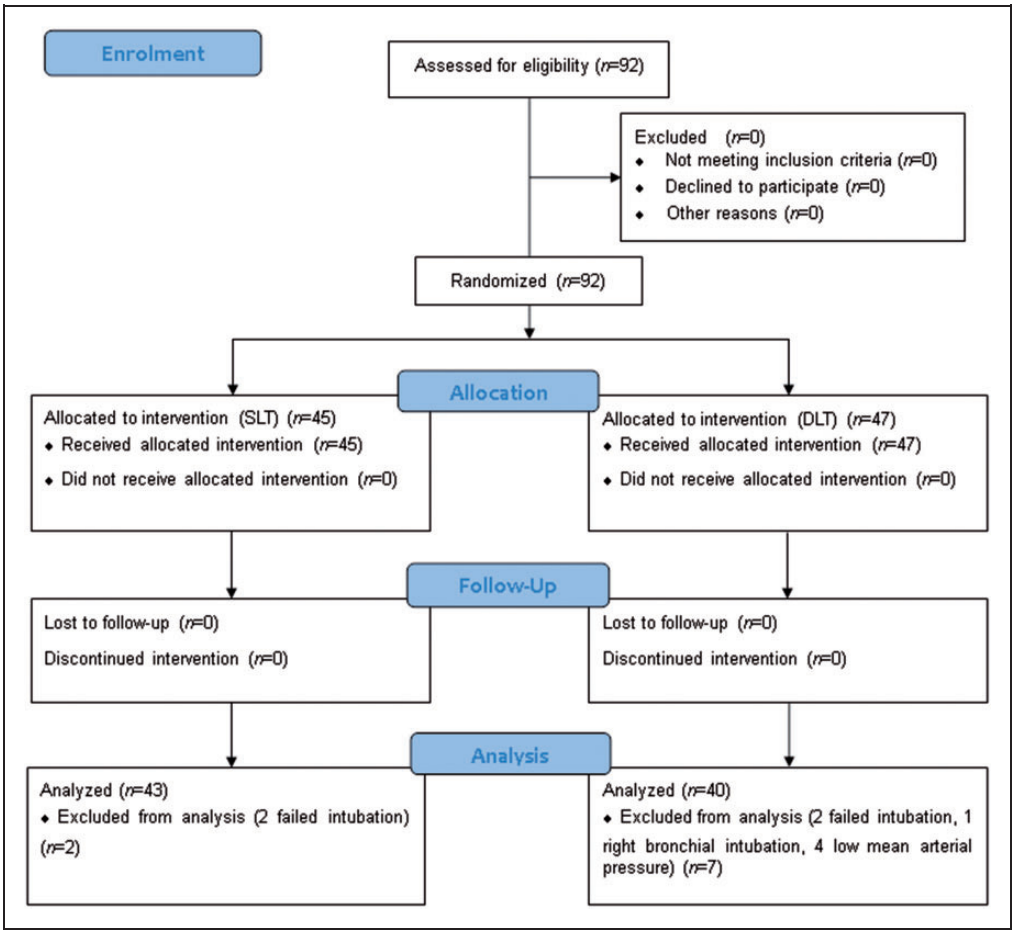

Figure 1. Flow diagram showing patient numbers at various stages of this randomized study that investigated the effect-site concentration of remifentanil required to blunt haemodynamic responses during tracheal intubation with a single-lumen tube (SLT) or double-lumen tube (DLT).

Table 1. Clinical and demographic characteristics of patients ($n = 83$) analysed in this randomized study that investigated the effect-site concentration of remifentanil required to blunt haemodynamic responses during tracheal intubation with a single-lumen tube (SLT) or double-lumen tube (DLT).

	SLT group $n = 43$	DLT group $n = 40$
Age, years	49.0 ± 11.8	50.5 ± 10.2
Sex, male	22 (51.2)	17 (42.5)
Height, cm	163.1 ± 8.1	163.4 ± 9.6
Weight, kg	61.3 ± 9.5	63.0 ± 12.3
Preoperative heart rate, beats/min	61.9 ± 8.9	61.1 ± 12.3
Preoperative mean arterial pressure, mmHg	63.7 ± 6.8	63.7 ± 8.9
Bispectral index value before intubation	47.8 ± 5.2	45.0 ± 6.6
Duration of intubation, sec	25.1 ± 5.3	33.4 ± 6.4*

Values are presented as mean ± SD or *n* of patients (%).
*$P < 0.001$ compared with the SLT group; Student's *t*-test.

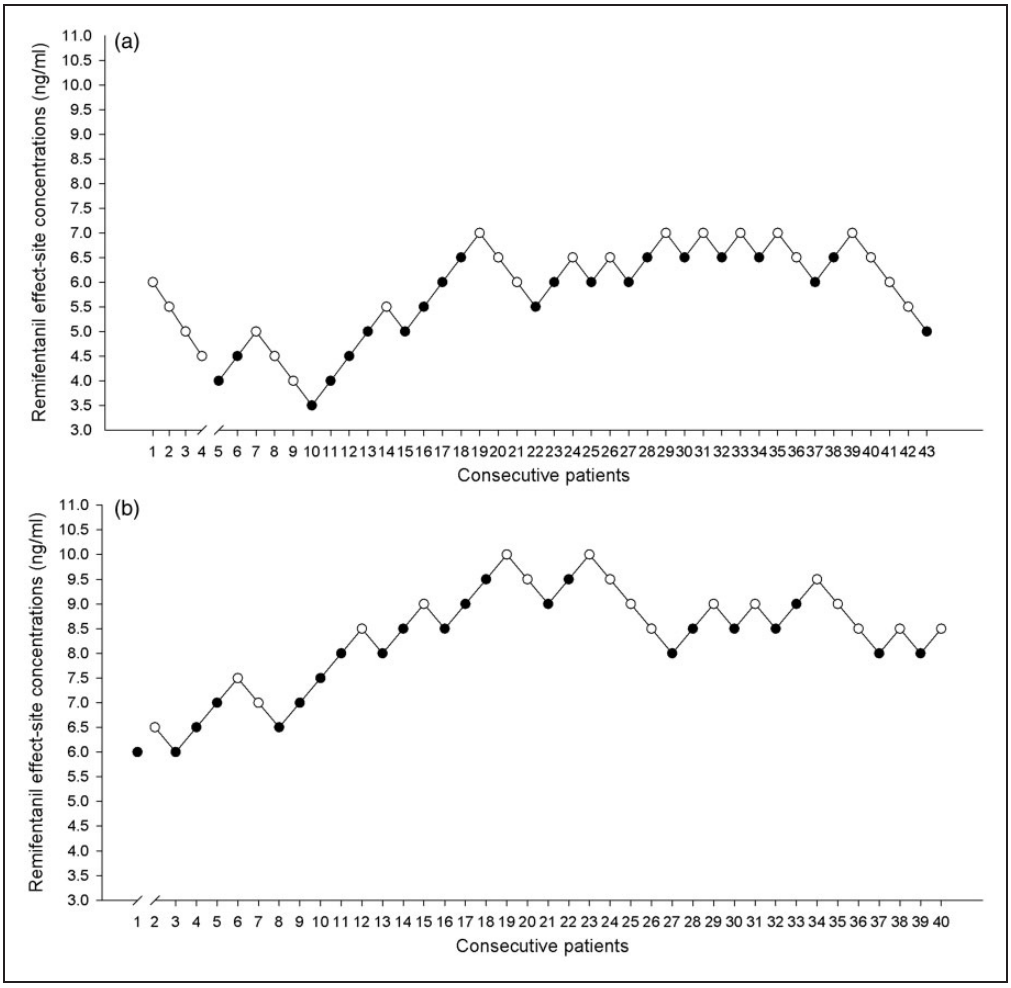

Figure 2. Sequences of the remifentanil effect-site concentration required to blunt haemodynamic responses. Single-lumen tube (a) and double-lumen tube (b) intubation. Positive (closed circle) or negative (open circle) haemodynamic responses during tracheal intubation were assessed by a delayed up-and-down sequential allocation method from consecutive patients with a predetermined concentration of remifentanil. The initial sequence of the same responses was truncated from the analysis to avoid bias from large first doses.

by isotonic regression with bootstrapping was higher in the DLT than in the SLT group (8.5 ng/ml [95% CI 8.0–9.5 ng/ml] versus 6.5 ng/ml [95% CI 5.6–6.7 ng/ml], respectively). Similarly, the EC_{95} in the DLT group was higher than in the SLT group (9.9 ng/ml [95% CI 9.8–10.0 ng/ml] versus 7.0 ng/ml [95% CI 6.9–7.0 ng/ml], respectively). Figure 3 shows the pooled adjacent-violators algorithm response rates for SLT and DLT intubation.

Discussion

Using a delayed up-and-down sequential allocation method, this present study demonstrated that a DLT requires a higher effect-site concentration of remifentanil than

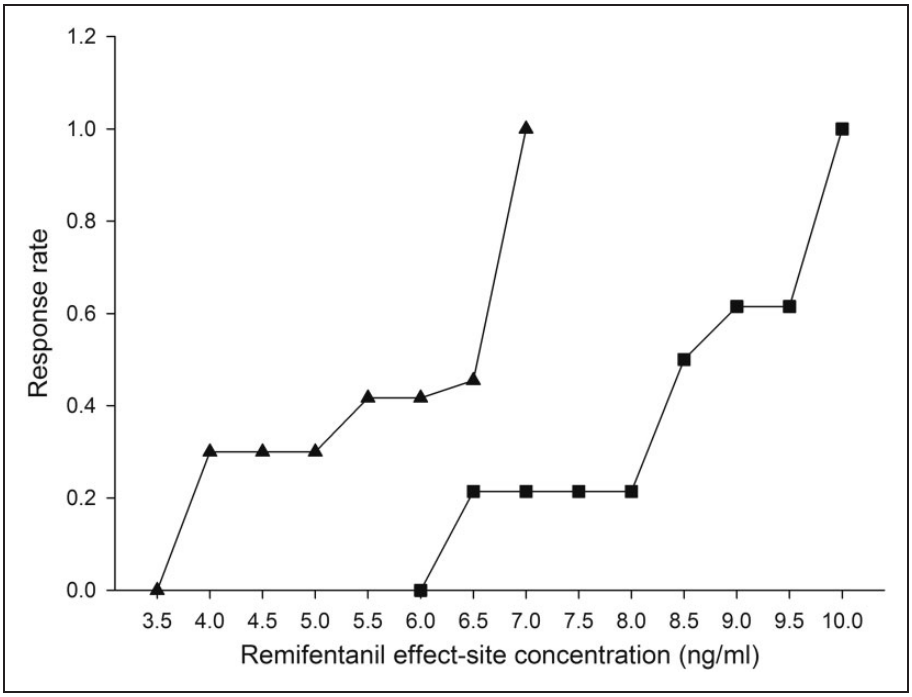

Figure 3. Pooled adjacent-violators algorithm response rate. The EC_{50} of remifentanil in the SLT (triangle) and DLT (square) groups was 6.5 ng/ml (95% confidence interval [CI] 5.6–6.7 ng/ml) and 8.5 ng/ml (95% CI 8.0–9.5 ng/ml), respectively. The EC_{95} in the SLT and DLT groups was 7.0 ng/ml (95% CI 6.9–7.0 ng/ml) and 9.9 ng/ml (95% CI 9.8–10.0 ng/ml), respectively. EC_{50}, effective effect-site concentration of remifentanil required to blunt haemodynamic responses in 50% of patients; EC_{95}, effective effect-site concentration of remifentanil required to blunt haemodynamic responses in 95% of patients; SLT, single-lumen tube; DLT, double-lumen tube.

does an SLT to blunt haemodynamic responses during tracheal intubation. The EC_{50} and EC_{95} of remifentanil required to blunt haemodynamic responses during tracheal intubation were 8.5 ng/ml (95% CI 8.0–9.5 ng/ml) and 9.9 ng/ml (95% CI 9.8–10.0 ng/ml) in the DLT group and 6.5 ng/ml (95% CI 5.6–6.7 ng/ml) and 7.0 ng/ml (95% CI 6.9–7.0 ng/ml) in the SLT group, respectively.

Airway stimulation and the associated haemodynamic stress response during tracheal intubation can be deleterious, especially in patients with cardiac or cerebrovascular disease.[16] Remifentanil is widely used in a clinical setting for its rapid onset and recovery, which enables easy titration for the intense stimulation experienced during tracheal intubation or extubation.[4,5,17] Thus, titrating the optimal remifentanil dose to blunt haemodynamic responses during DLT intubation is clinically important. To the best of our knowledge, this is the first randomized study to compare the effective effect-site concentration of remifentanil between SLT and DLT intubation.

The EC_{50} of remifentanil for blunting haemodynamic responses during SLT tracheal intubation appeared to be at least 5.8 ng/ml, which was higher than that reported by a previous study,[5] which

proposed an effect-site concentration of 5 ng/ml. This difference is probably due to differences in the patient population, tracheal tube size, or study methodology. Another possibility is that the continuous arterial pressure monitoring used in this study more sensitively detects haemodynamic responses during tracheal intubation than does the non-invasive blood pressure monitoring used in the previous study.[5]

In the present study, the EC_{50} of remifentanil in the DLT group was approximately 30% higher than in the SLT group. One of the major reasons for the higher remifentanil requirements during DLT intubation is the large tracheal diameter of DLTs. A larger tracheal tube size is correlated with a sore throat and hoarseness.[18,19] Larger tubes and proportionately larger cuffs may cause a greater area of laryngeal and carinal stimulation due to the larger contact area. Secondly, the stiff stylet that is provided with the DLT for ease of proper tracheal tube placement may further stimulate the airway. In this present study, we used the default stylet during the DLT intubation, but did not use the stylet during SLT intubation. Thirdly, DLT intubation generally requires a longer time for tube placement than does SLT intubation because it requires one more step of bronchial intubation. There is a linear relationship between the degree of blood pressure elevation and intubation time in direct laryngoscopy.[20] In this present study, the intubation time was significantly longer in the DLT group than the SLT group (33.4 ± 6.4 versus 25.1 ± 5.3 s, respectively; $P < 0.001$), which might lead to a higher EC_{50} of remifentanil in the DLT group.

The estimated EC_{95} of remifentanil required to blunt haemodynamic responses during tracheal intubation is of clinical interest. This value was estimated as 7.0 ng/ml in the SLT group and 9.9 ng/ml in the DLT group in this study. Due to its rapid onset and clearance, large doses of remifentanil can be administered to prevent noxious stimulation without compromising rapid recovery.[21] However, high-dose remifentanil may raise concerns because it can cause hypotension and bradycardia.[4] Thus, dose reductions in remifentanil should be considered in compromised elderly patients.

There were several limitations to the present study. First, it used isotonic regression to estimate the EC_{95}. However, an extrapolation of the EC_{95} from small up-and-down data can be imprecise at the upper part of the distribution.[14] Secondly, the remifentanil concentration was limited to a fixed concentration of propofol, although the target dose is commonly used in clinical practice.[5,7,10] Propofol reduces the remifentanil requirements for suppressing responses in a synergistic manner.[22] Thus, the effective effect-site concentration of remifentanil can differ at other target concentrations of propofol. Thirdly, the study did not measure the actual plasma remifentanil concentration. However, the remifentanil effect-site concentration was predicted via the Minto pharmacokinetic model, which has been shown to be accurate in predicting effect-site concentrations.[9]

In conclusion, this present study demonstrated that a DLT requires a 30% higher EC_{50} of remifentanil than does an SLT to blunt haemodynamic responses during tracheal intubation when combined with a BIS-guided target-controlled infusion of propofol.

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Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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