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Original Article

The median effective concentration of remifentanil to inhibit pupillary reflex dilation induced by endotracheal intubation

Meijuan Qian[1], Yue Zhao[1], Li Han[1], Lihong Zhao[1], Fen Yang[1], Hong Xie[2], Yang Xie[1]

[1]Department of Anesthesiology, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Gusu School of Nanjing Medical University, Suzhou 215002, Jiangsu, China; [2]Department of Anesthesiology and Critical Care, The Second Affiliated Hospital of Soochow University, Suzhou 215008, Jiangsu, China

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Abstract: Objective: To determine the median effective concentration (EC_{50}) of remifentanil to inhibit pupillary reflex dilation (PRD) induced by endotracheal intubation using a modified sequential test method. Methods: In this prospective study, 34 patients undergoing elective surgery under general anesthesia were selected. The induction of anesthesia was started using propofol with an effect-site concentration (Ce(pro)) of 4.0 μg/mL. The effect-site concentration of remifentanil (Ce(Remi)) was set according to the modified sequential test method, with 0.42 ng/mL as the initial concentration for the first patient. The gradient ratio was 1.1. The Ce(Remi) of each patient was determined by whether the PRD of the previous patient disappeared during endotracheal intubation. If the PRD disappeared, a lower concentration was applied. Otherwise, a higher concentration was applied. The experiment ended after 9 crosses of PRD disappearance-presence and PRD presence-disappearance. The EC_{50} of remifentanil and 95% confidence interval (CI) were calculated using the Dixon and Massey's method. The Probit regression procedure was used to derive the EC_{50}, 95% effective concentration (EC_{95}) of remifentanil and their 95% CIs. Results: The EC_{50} of remifentanil to inhibit PRD induced by endotracheal intubation was 4.41 ng/mL (95% CI, 4.32 to 4.49 ng/mL) and the EC_{95} was 5.24 ng/mL (95% CI, 4.78 to 7.68 ng/mL). In 34 patients, the time to reach the maximum change in heart rate, systolic blood pressure, mean arterial pressure and Bispectral index was 75.00 (60.00-98.00) s, 95.00 (75.00-133.00) s, 95.00 (75.00-135.00) s, and 100.00 (78.00-113.00) s, respectively, which was significantly longer than the time (42.00 (25.00-47.00) s) needed for pupillary diameter ($P<0.05$). Conclusion: The EC_{50} of remifentanil to inhibit PRD induced by endotracheal intubation was 4.41 ng/mL and the EC_{95} was 5.24 ng/mL. The time to reach the maximum pupillary diameter change was shorter than the time needed for heart rate, blood pressure, and Bispectral index. This prospective study was registered in the China Clinical Trials Registration Center (ChiCTR2100043771, https://www.chictr.org.cn).

Keywords: Ultrasound, pupils, remifentanil, sequential method, endotracheal intubation

Introduction

In patients under anesthesia, the speed and amplitude of the pupillary reflex dilation (PRD) due to stimulation are affected by various factors. As sedation deepens, the pupil gradually shrinks [1]. The amplitude of the PRD is proportional to the intensity of the nociceptive stimulus [2]. Previous studies have shown that in both awake patients and those receiving propofol or volatile anesthetics, the amplitude of PRD is proportional to the intensity of nociceptive stimulus, but is inversely related to the amount of opioids [2-4]. The combination of opioids, like remifentanil with propofol is currently considered as the best combination of total intravenous anesthesia [5]. It is suitable to apply target-controlled infusion (TCI) of remifentanil with propofol during induction to provide stable plasma drug concentrations, and simulate stable effect-site concentrations [6]. Recently, Joint Guidelines from the Association of Anaesthetists and the Society for Intravenous Anaesthesia have pointed out when TCI of remifentanil is used with propofol, a target concentration of remifentanil is 2 to 6 ng/ml (equivalent to 0.08

to 0.25 μg.kg^{-1}.min^{-1}) and that the administration rate of propofol and remifentanil is adjusted based on clinical symptoms during anesthesia maintenance [7]. In addition, according to the recommended dosage of remifentanil, patients (12 to 65 years old) are induced with 0.5 to 1 μg/kg, at a rate of 0.25±0.03 μg.kg^{-1}.min^{-1}, and the individualized infusion rate is between 0.05 and 2 μg.kg^{-1}.min^{-1}. In Douglas's study, within the initial three minutes of induction, a target-controlled-infusion (TCI) Minto model for remifentanil was used [8], and the drug dose was consistent with that recommended in the instruction when the target concentration was about 4.0 ng/mL. It is estimated that 3.1 to 5.3 ng/mL is appropriate for the initial dose; however, the confirmed target concentration of TCI of remifentanil is only approximate to the recommended dosage in the instructions, which does not necessarily achieve the expected clinical effect [8]. In order to use PDR suppression as a clinical endpoint for evaluating the effects of opioid analgesia, a reasonable threshold must be set like other indicators such as the pupillary pain index (PPI), pupillary light reflex (PLR), and pupillary unrest under ambient light (PUAL) [9]. Aissou's study showed that in the early postoperative period, pupils that were dilated by 23% predicted a verbal pain score of more than 1 point, with a sensitivity and specificity of 91% and 94%, respectively [3]. In this study, the half effective concentration (50% effective concentration, EC_{50}) of pupillary reflex dilation (PDR) induced by intubation was determined by a modified sequential method using different effector target concentrations of remifentanil according to whether the magnitude of pupillary dilation exceeded 23% as the threshold, and the 95% effective concentration (EC_{95}) was estimated by the probability unit regression method (Probit).

Materials and methods

General data

A total of 34 patients undergoing elective surgery under general anesthesia in Suzhou Hospital Affiliated with Nanjing Medical University from January to April in 2022 were prospectively analyzed in this study. This study was approved by the Ethics Committee of Suzhou Hospital Affiliated to Nanjing Medical University (approval number SZSLYY-2022-106-01). All the patients signed an informed consent form.

Inclusion criteria: (1) Patients were aged from 18 to 65 years old. (2) Patients were graded by the American Society of Anesthesiologists (ASA) Classification between I-II. (3) Patients' body mass index ranged from 18 to 28 kg/m^2. (4) Patients had normal results in preoperative examinations (electrocardiogram, lung function, liver and kidney function, electrolytes, hemoglobin, platelets, and routine preoperative coagulation screening). (5) Patients had no eye disease, no history of opioid abuse or allergies, nor history of antileptic drug abuse and allergies. (6) Patients had no chronic diseases such as coronary heart disease, severe heart rate aberration (including atrial fibrillation), and chronic bronchitis. (7) Patients had no neurological and psychiatric disorders. (8) Patients had no potentially difficult airways (cervical spondylosis, Mallampati grade III or above, mouth opening less than 3.5 cm, thyromental distance less than 6.5 cm, cervical retrovertebral difficulty, etc.).

Exclusion criteria: (1) Patients who underwent surgeries under general anesthesia combined with intraspinal anesthesia or regional nerve block. (2) Patients' BMI>30 kg/cm^2. (3) Patients who took sedative analgesics and psychotropic drugs for a long time. (4) Patients who were given anticholinergic drugs before surgery. (5) Patients who took sympathetic or parasympathetic cardiovascular active drugs for a long time. (6) Patients who had history of eye disease or eye surgery. (7) If patients' bilateral pupillary sizes were unequal. (8) Patients who suffered from previous cranial neuropathy. (9) Patients had mutilated arms.

Elimination criteria: (1) Patients with difficulty in exposing their glottis or with difficult airways. (2) Patients with intubation time more than 2 minutes. (3) Patients with mean arterial pressure (MAP) <50 mmHg or heart rate (HR) <45 beats/min during the induction. (4) Patients who used vasoactive drugs. (5) Patients with TCI pump failure resulting in inestimable plasma drug concentration.

Anesthesia regimen

All patients were fasted for 8 h before surgery and abstained from drinking for 4 h, including preoperative medication. After the patients entered the room, the venous channel was opened, and the ECG, pulse oximetry, noninva-

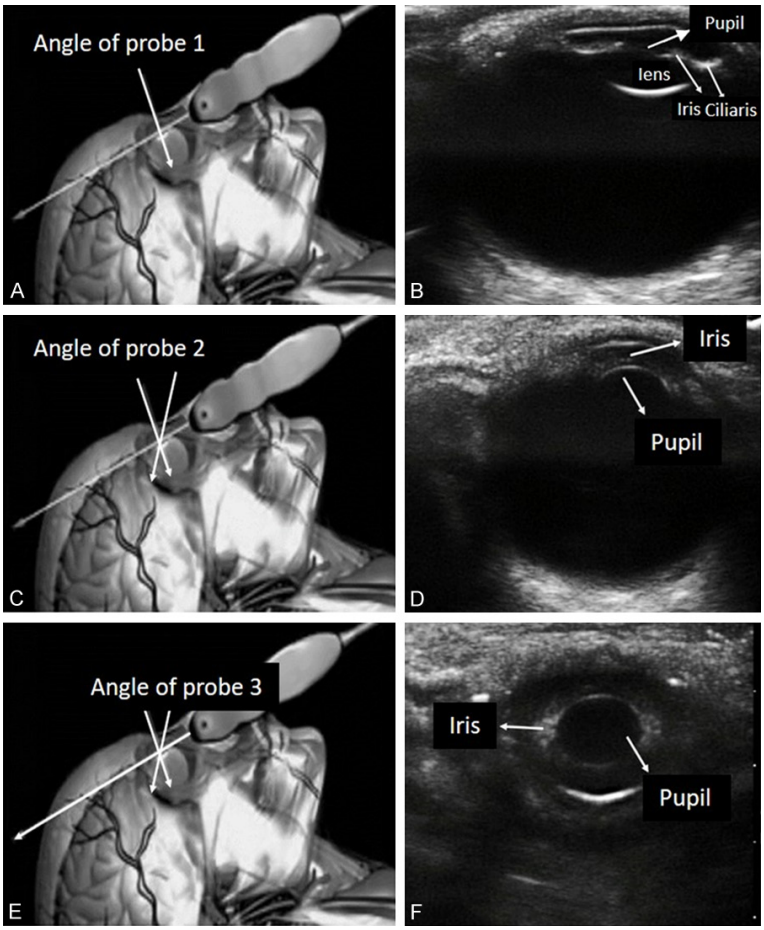

Figure 1. Angle of probes and ultrasound images. A: Angle of probe 1: the probe was perpendicular to the face; B: Ultrasound image of the eye under the angle of probe 1; C: Angle of probe 2: the probe was 45° to the face; D: Incomplete pupil image at the angle of probe 2; E: Angle of probe 3: the probe was close to the face; F: Complete pupil image at the angle of probe 3.

sive blood pressure, and Bispectral index (BIS) monitoring were initiated. The effect-site concentration of propofol (Ce(pro)) was set to 4 μg/mL [6]. The oxygen mask was put on for 5 min and Ringer's lactate solution (10 mL/kg/h, 21K1608, Guangdong Otsuka Pharmaceutical Co., Ltd.) was infused intravenously.

The induction of anesthesia was started using propofol (RA225, AstraZeneca) with Ce(pro) of 4.0 μg/mL. After the patient lost consciousness, blood pressure was measured quickly. TCI of remifentanil (00B02110, Yichang Humanwell Pharmaceutical Co., Ltd.) was started, followed by intravenous injection of 0.6 mg/kg rocuronium bromide (210708, Zhejiang Xianju Pharmaceutical Co., Ltd.) within 5 s. Endotracheal intubation was carried out 2 min after TCI of remifentanil. Propofol was adjusted to maintain the BIS between 40 and 60 before intubation. In conditions of breathing difficulties occured, the oxygen mask and manual artificial respiration were utilized until endotracheal intubation.

Ultrasound video was recorded after stable images were obtained (see below for specific methods). Meanwhile, endotracheal intubation was initiated and performed by a formally trained anesthesiologist. An endotracheal cuff with an inner diameter (ID) of 7.5 mm was used for male patients and an ID of 7.0 mm for female patients. Video laryngoscope was utilized for endotracheal intubation. The procedures were in sequence of placing laryngoscopes, picking epiglottis, placing the endotracheal catheter through the glottis, forwarding the tube 1-2 cm to the throat, inflating the cuff (6 ml for men, 5 mL for women) to fix the catheter, and connecting the ventilator for mechanical ventilation. The medical workers worked gently to keep the ultrasound image stable. Endotracheal intubation was started with the insertion of laryngoscopy and ended with the connection of a ventilator. During the induction period, the pupil was observed with ultrasound. At the beginning of endotracheal intubation, ultrasound video of pupillary changes was simultaneously recorded for at least 2 min. HR, blood pressure, and BIS after intubation were continuously measured and observed for 3 min.

Ultrasound observation of the pupil

The operating room light was adjusted in advance. The linear probe was placed parallel to the patient's lower eyelid. The probe was slightly tilted towards the face, pointing to the head (**Figure 1**). The assistant was instructed to click and save the clear images of the iris and pupil coronal surface. Another doctor was

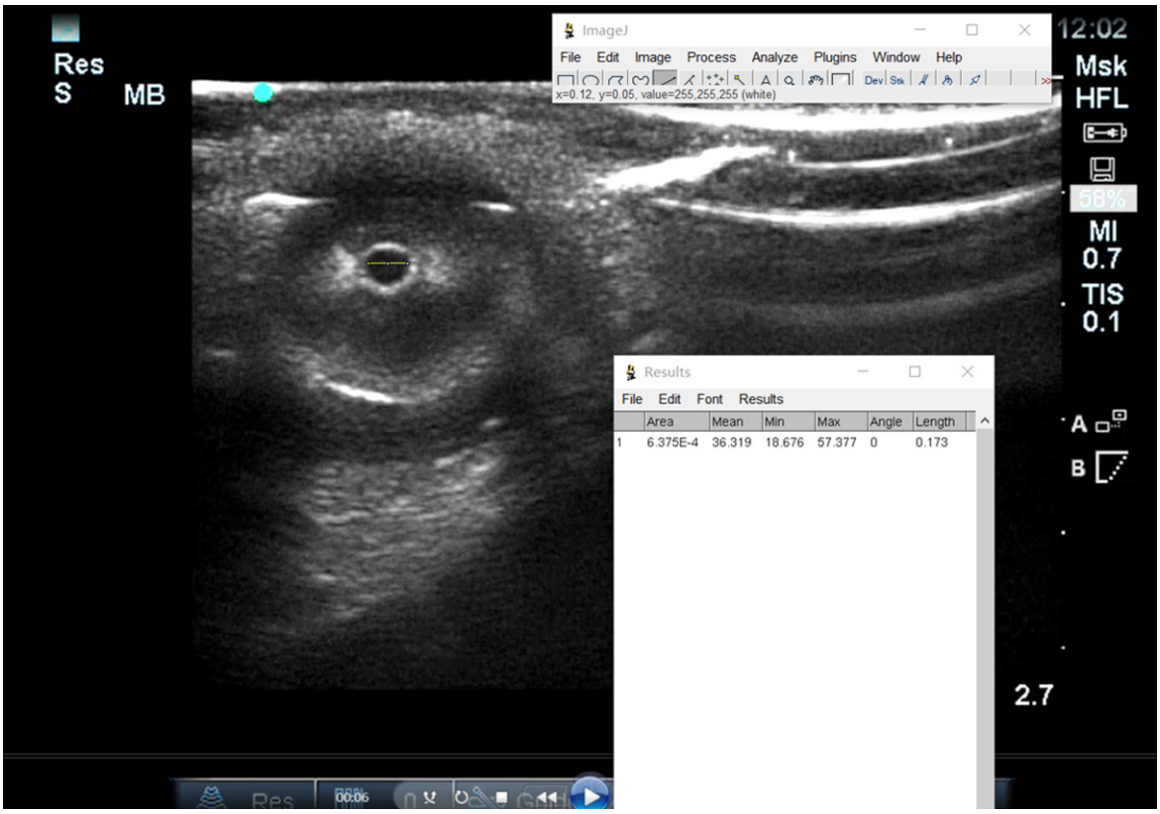

Figure 2. Acquisition and measurement of pupillary images.

responsible for data collection and processing. The largest and smallest pupillary diameters (PD, at least 10 times before and after pupil changes in each video) in the PRD that were captured by the ultrasound image were measured by Image J 2016. The PD could be accurate to 0.001 cm in this way (**Figure 2**).

Outcome measures

Before induction, light measuring equipment was used to measure the intensity of light above the patient's eyes. The PD was measured three times in a row to obtain the average. Indicators, such as PD, HR, systolic blood pressure (SBP), MAP and BIS were recorded as PD0, HR0, SBP0, MAP0 and BIS0 when patients were in the awake state, and as PD1, HR1, SBP1, MAP1 and BIS1 before endotracheal intubation. The maximum value after endotracheal intubation were marked as PD2, HR2, SBP2, MAP2 and BIS2. The time to maximum change in these indicators were recorded as T_{PD}, T_{HR}, T_{SBP}, T_{MAP} and T_{BIS}. Maximum change rate in PD was regarded as ΔPD% (ΔPD% = (PD2-PD1)/PD1). In the same way, ΔHR% = (HR2-HR1)/HR1, ΔSBP% = (SBP2-SBP1)/SBP1, ΔMAP% = (MAP2-MAP1)/MAP1, and ΔBIS% = (BIS2-BIS1)/BIS1 were used to present maximum change rates for relevant indicators.

Statistical analyses

According to the rules of the sequential test method, a typical sample size of less than 35 was estimated for performance similar to a fixed-dose design, so sample size of 35 was initially estimated [10]. Finally, 34 eligible patients were included in the study. SPSS 26.0 software, Excel 2018 and GraphPad Prism 9 were adopted to process the data. The Shapiro-Wilk test was used to check the normal distribution of continuous variables. Measurement data with normal distribution were expressed as mean ± standard deviation ($\bar{x}$ ± sd), and those with non-normal distribution were expressed as median (quartile range). Comparison of parameters was carried out using t-test and one-way analysis of variance. As for nonparametric data, two independent samples were analyzed using the Mann-Whitney U test while multiple independent samples were analyzed

Table 1. General data of the included patients

Ce(Remi)	Male/Female	Age (years old)	Weight (kg)	Height (cm)	PD0 (mm)	Luminous intensity (LUX)
3.47 ng/mL	0/1	42.0	55.32	161.21	4.81	118.31
3.82 ng/mL	1/3	45.5±10.7	60.81±6.28	164.61±4.27	4.68±0.04	115.29±12.38
4.20 ng/mL	4/7	43.7±12.3	61.23±4.96	163.61±5.68	4.32±0.05	119.73±14.46
4.62 ng/mL	7/6	44.3±16.8	67.86±3.43	166.93±6.78	4.57±0.03	118.56±15.43
5.08 ng/mL	4/1	43.6±14.3	69.21±5.11	168.54±6.82	4.69±0.04	117.84±16.11

Note: Ce(Remi): effect-site concentration of remifentanil; PD: pupillary diameter.

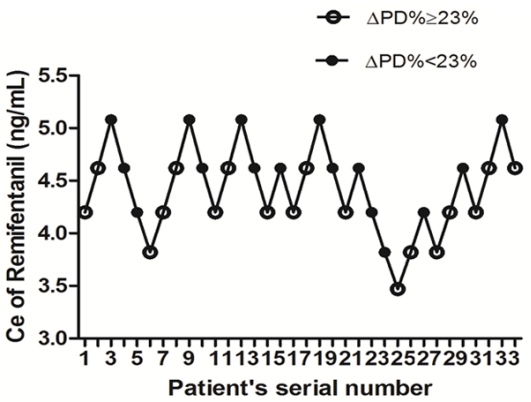

Figure 3. Curve of Ce(Remi) on inhibiting the PRD induced by endotracheal intubation. Assessment of negative or positive responses to inhibit PRD induced by endotracheal intubation under a predetermined Ce(Remi) using the Dixon "up-and-down" method in 34 consecutive patients. Horizontal bars represent crossover midpoints (negative to positive). Ce(Remi): effect-site concentration of remifentanil.

using the Kruskal-Wallis test. Chi-square was adopted for comparison of categorical variables. The EC_{50} and 95% CI of remifentanil were calculated using the Dixon and Massey's method. The Probit regression procedure was used to evaluate the EC_{50}, EC_{95} and their 95% CIs of remifentanil [11]. After inputting the data, we adopted the Condensation analyses t test, nonparametric test and Probit regression. Pearson chi-square test was used to assess goodness of fit (P>0.05 indicates goodness of fit). If the P<0.05 in a two-tailed test, the difference was considered statistically significant.

Results

General information of the included patients

Thirty-five patients were enrolled in the study. During the study, one patient was eliminated because of difficulty in exposing the glottis and inability to keep stable ultrasound images. Thirty-four patients, including 16 males and 18 females who completed this experiment, were included in this study. See **Table 1**.

Effect of remifentanil on inhibiting the PRD induced by endotracheal intubation

The effect-site concentration of remifentanil (Ce(Remi)) was set according to the modified sequential test method, with 0.42 ng/mL as the initial concentration for the first patient. The gradient ratio was 1.1. The Ce(Remi) of each patient was determined by whether the PRD of the previous patient disappeared during endotracheal intubation. ΔPD% less than 23% was defined as PRD disappearance, suggesting remifentanil was effective in inhibiting intubation-induced PRD. If the PRD disappeared, a lower concentration was applied. Otherwise, a higher concentration was applied. The experiment ended after 9 crosses of PRD disappearance-presence and PRD presence-disappearance.

Figure 3 shows Ce(Remi) determined by ΔPD% at the time of intubation in 34 patients according to the rules of the sequential method.

EC_{50}, EC_{95} of remifentanil to inhibit PRD induced by endotracheal intubation

The number of effective cases (s) and ineffective cases (r) of Ce(Remi) inhibiting intubation stimulation were recorded. The difference between the logX of each dose and the total cases of effective and ineffective inhibition of intubation stimulation at that dose (n) were calculated. The effective rate (P), and the log number of doses of two adjacent gradients (d = 0.041) were also calculated. See **Table 2**.

The logarithm of EC_{50}: $\log EC_{50} = \sum n\log X/\sum n$. The antilogarithm was presented for EC_{50}.

The standard error of EC_{50}: $SIEC_{50} = d\sum P(1P)/(n-1)$.

Table 2. The EC_{50} of remifentanil to inhibit PRD induced by endotracheal intubation were calculated using the Dixon and Massey's method

X	LogX	s	r	n	P	nlogX	P(1-P)/(n-1)
3.47	0.540	0	1	1	0	0.540	
3.82	0.582	1	3	4	0.250	2.328	0.063
4.20	0.623	3	8	11	0.273	6.853	0.020
4.62	0.665	7	6	13	0.538	8.645	0.021
5.08	0.706	5	0	5	1	3.530	
Total				34		21.896	0.104

Note: EC_{50}: median effective concentration; PRD: pupillary reflex dilation.

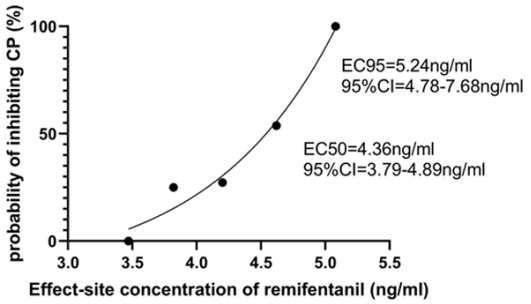

Figure 4. Effect-site concentration and response curves from the Probit analysis in patients. The EC_{50} and EC_{95} of remifentanil (95% confidence interval) required to inhibit PRD induced by endotracheal intubation were 4.36 (3.79-4.89) ng/mL and 5.24 (4.78-7.68) ng/mL, respectively. EC_{50}: median effective concentration; EC_{95}: 95% effective effect-site concentration.

The 95% CI of EC_{50}: $\log^{-1}$(log EC_{50}-1.9 log 6S log EC_{50}, log EC_{50}+1.96S log EC_{50}).

As a result, the EC_{50} was 4.41 ng/mL, and 95% CI was 4.32-4.49 ng/mL.

The probability formula for remifentanil endotracheal intubation was Probit (*p*) = -8.13+ 3.62X.

Probit was used to evaluate the EC_{95} of remifentanil and 95% CI

From the Probit regression procedure, the EC_{50} of remifentanil to inhibit PRD caused by endotracheal intubation was 4.36 ng/mL (95% CI, 3.79-4.89 ng/mL), and the EC_{95} was 5.24 ng/mL (95% CI, 4.78-7.68 ng/mL). The chi-square goodness of fit test showed χ^2 = 3.559 and P = 0.347. See **Figure 4**.

Table 3. Time to reach the maximum changes in PD, HR, SBP, MAP, and BIS within 3 minutes after endotracheal intubation

Item	Time (s)
T_{PD}	42.00 (25.00~47.00)
T_{HR}	75.00 (60.00~98.00)*
T_{SBP}	95.00 (75.00~133.00)*
T_{MAP}	95.00 (75.00~135.00)*
T_{BIS}	100.00 (78.00~113.00)*

Note: PD: pupillary diameter; HR: heart rate; SBP: systolic blood pressure; MAP: mean arterial pressure; BIS: Bispectral index. T: time. Compared with T_{PD}, *P<0.05.

Table 4. The maximum change rate of each index within 3 minutes after endotracheal intubation

Index	Change rate (%)
ΔPD%	17.87 (12.23~28.89)
ΔHR%	21.54 (15.36~39.76)
ΔSBP%	16.41 (7.62~25.32)
ΔMAP%	16.37 (9.21~27.45)
ΔBIS%	12.63 (5.67~21.43)

Note: PD: pupillary diameter; HR: heart rate; SBP: systolic blood pressure; MAP: mean arterial pressure; BIS: Bispectral index. Compared with ΔPD%, P>0.05.

Comparison of the maximum time needed for PD, HR, SBP, MAP, and BIS within 3 minutes after endotracheal intubation

Overall, in 34 patients, the time required to reach PD2 was shorter than the time needed for HR2, SBP2, MAP2, and BIS2 (P<0.05). See **Table 3**.

The maximum change rate of each indicator within 3 minutes after endotracheal intubation

There was no statistical difference in the maximum change rate of HR, SBP, MAP, and BIS in 34 patients, as compared with that in PD (P>0.05). See **Table 4**.

Discussion

Anesthesia induction with propofol and remifentanil (TCI) has been used in a variety of small surgeries, such as surgeries for vocal cord polyps, and esophageal foreign bodies. Laryngoscope and endotracheal intubation can cause severe cardiovascular response. During the procedure, the vocal cords are required to

remain as stationary as possible, thus laryngeal reflexes should be suppressed and the muscles should be completely relaxed. It is also required that patients recover and revive from the operation as soon as possible and prevent aspiration of airway secretions [12-14]. Therefore, it is crucial to establish a more scientific approach to determine a reasonable dose of anesthetic in surgery. As one of the common tools in clinical work, ultrasound has the advantages of simple operation, being non-invasive and easy to obtain. Ultrasound can be used for eye structure examination. Some portable ultrasound devices are even equipped with professional ophthalmic models. Currently, there are growing studies on the use of pupillary size in the monitoring of nociceptive sensation. However, the use of ultrasound to measure PD and its application to patients under general anesthesia are rarely reported. Based on the previous judgment of the depth of anesthesia and the degree of noxious stimulation, this study used the advantages of ultrasound (non-invasive, real-time, accurate and able to provide quantitative data) to observe the changes of the pupils of patients in real time. Besides, the pupillary change rate was considered as a judgment index. The half-effective dose of analgesics during endotracheal intubation was observed under analgesia.

In a previous study, the EC_{50} of BIS-guided remifentanil to inhibit the cardiovascular response to intubation stimulation was 4.6 ng/mL and the EC_{95} was up to 6.0 ng/mL [15]. The later was significantly higher than the recommended doses in the instructions [16]. In Andrea's study, the EC_{50} of BIS-guided remifentanil to inhibit cardiovascular responses induced by tracheal intubation and incisional stimulation were 5.0 and 2.1 ng/mL, respectively [17, 18]. Liu also calculated the EC_{50} of remifentanil to inhibit the cardiovascular response induced by laryngoscope. TCI of remifentanil was performed first, followed by the propofol, resulting in a EC_{50} dose of 3.5 ng/mL [19]. In this study, in patients receiving BIS-guided propofol, when Ce(Remi) was achieved and maintained at 4.41 ng/mL in the initial induction stage, 50% of patients had a weakened PRD caused by intubation. Obviously, it is not clinically practical. The stress response in all patients must be controlled. Thus, the Probit regression procedure was used to evaluate the EC_{95} of remifentanil, with a result of 5.24 ng/mL. It was not only within the recommended dosage range of the instructions, but also weakened the cardiovascular response and PRD caused by intubation in most patients, reaching clinical achievements. Therefore, we recommend the use of 5.24 ng/mL of remifentanil for induction, which was less than the dosage in the other studies.

In our study, the change of PD was significantly faster than the changes of HR, BP, and BIS in terms of time, with no statistical difference in the amplitude of change. Therefore, it is speculated that the pupil has a quick response to the intubation stimulation, but without a clear advantage in the amplitude of change. However, a study including 150 patients in surgical excision has revealed that the change amplitude of HR and SBP is less than 15%. When the ΔPD% is less than 44.5% and 46.5%, the sensitivity and specificity of the two are 89.7%, 92.5% and 88.6%, 89.1%, respectively [20]. As for stimulation from skin incision, when the change in HR and BP is less than 15%, the ΔPD% is about 45%. In our study, in terms of intubation stimuli, when ΔPD% was less than 23%, the change in HR and BP was about 20%. From this, it was speculated that skin incision stimulation may cause PRD, while intubation stimulation may cause more cardiovascular responses than PRD. The cardiovascular response and the pupillary dilation response are autonomous responses of the sympathetic and parasympathetic nerves; however, PRD takes significantly less time to reach the maximum than the cardiovascular response in terms of response time [21, 22]. This may be because compared to heart and large blood vessel smooth muscles, it is easier to mobilize the small pupil dilated muscles and sphincter muscles in a short period of time, and the pupil changes more rapidly, but the specific mechanism still needs to be illustrated with more basic research. Pupillary size is determined by the balance between sympathetic tone and parasympathetic contractile tone [23, 24]. The pupil diameter of patients under general anesthesia is 1.5-2.5 mm. When skin incision or the establishment of the pneumoperitone is performed, nociceptive stimulation activates neuronal cells in the brainstem reticular structure and inhibits the Edinger-Westphal (EW) nucleus of the midbrain [25-27]. The pupil dilates passively with inhibition of the sphincter. These

inhibitory neurons are activated by the state of nociception and arousal, but their action on EW cells is blocked by opioids [28, 29]. The correlation between pupillary changes and the degree of analgesia in patients still needs further study.

This study still has some limitations. First, this is a single-center, double-blind randomized study, and studies with multiple centers and more samples are needed to reduce bias. Second, we used a modified sequential method with a small sample size to establish a rough EC_{50}, which was affected greatly by individual differences. Third, the accuracy of EC_{95} using the Probit remains to be examined, and there may be better mathematical models [30, 31]. Fourth, we did not take blood samples to measure the actual blood concentration of remifentanil but simply simulated a stable Ce(Remi) using the Minto pharmacokinetic model, which is widely used in clinical settings but is always subject to some bias [32, 33]. Although we used a fixed propofol concentration of 4 μg/mL and maintained the pre-stimulation BIS level between 40 and 60, there may still be differences in the degree of sedation of BIS between 40 and 60, and we cannot completely rule out the effect of sedation depth on PRD.

In conclusion, the EC_{50} of remifentanil to inhibit PRD induced by endotracheal intubation was 4.41 ng/mL and the EC_{95} was 5.24 ng/mL. The time to maximum PD was shorter than the time needed for HR, SBP, and BIS.

Disclosure of conflict of interest

None.

Address correspondence to: Yang Xie, Department of Anesthesiology, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Gusu School of Nanjing Medical University, No. 26 Daoqian Street, Gusu District, Suzhou 215002, Jiangsu, China. Tel: +86-1360-6212680; E-mail: xieydoctor@126.com

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