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Target propofol concentration required for laryngeal mask airway insertion after pretreatment with dexmedetomidine

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The aim of this study was to determine the target-controlled concentration of propofol required for successful laryngeal mask airway (LMA) placement after dexmedetomidine pre-injection. Twenty ASA physical status I–II patients aged 20–60 years old, who were scheduled for general anesthesia, were studied. After receiving a loading dose of 1.0 μg/kg dexmedetomidine over 10 min, propofol was infused using a target-controlled infusion as determined by a modified Dixon's up-and-down method. The first patient received a target-controlled infusion of 3.0 μg/ml propofol. The response of each patient determined the propofol concentration given to the next patient. Cough, body movement, laryngospasm, intentional movement, mouth opening, and difficulty of LMA insertion indicated failure, and the propofol concentration was increased by a step of 0.2 μg/ml. If the insertion of the LMA was successful, then the target concentration was decreased by the same dose. The effect-site propofol concentration for successful LMA insertion was determined to be 2.351 μg/ml in 50% of the patients (EC50) with pre-injection of dexmedetomidine without muscle relaxant. Subsequent probit analysis showed an EC95 (95% CI) of 2.854 μg/ml (2.588–2.944 μg/ml). Thus, dexmedetomidine combined with target-controlled infusion of propofol can be used for LMA placement, with few adverse reactions. In addition, dexmedetomidine sedation can effectively reduce the target-controlled plasma concentration of propofol.

Key words: Dexmedetomidine, propofol, target-controlled infusion, laryngeal airway mask.

INTRODUCTION

A laryngeal mask is widely used in clinical anesthesia to establish an effective airway. Successful insertion of a laryngeal mask airway (LMA) requires an adequate depth of anesthesia to reduce the laryngeal response and prevent coughing, laryngospasm, and other adverse events. Propofol is a short-acting intravenous anesthetic that can effectively reduce laryngeal responses and is widely used to induce anesthesia for laryngeal mask placement (Wang et al., 2010). However, anesthetic induction using propofol alone often requires large doses to achieve enough depth of anesthesia for LMA insertion, resulting in hemodynamic fluctuations and transient respiratory depression. Clinical trials have shown that separate applications (2.5–3 mg/kg) or plasma concentrations (7–9 μg/ml) of propofol cannot meet the LMA insertion anesthetic requirements (Hickey et al., 1990; Higuchi et al., 2002; Richebe et al., 2005; Taylor and Kenny, 1998). To avoid this problem, propofol is usually combined with other drugs like fentanyl or remifentanil.

Dexmedetomidine is a highly selective, α2 receptor agonist with sedative and analgesic properties. It reduces the amount of anesthetic required and provides

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hemodynamic stability without respiratory depression. The purpose of this study was to determine, following premedication with dexmedetomidine, the optimal plasma concentration of propofol required for successful laryngeal mask placement.

MATERIALS AND METHODS

After approval from the ethics committee of Jilin University and patients' written informed consent, 22 patients, ASA status I–II, aged 20 to 60 years old, were included in the study. Patients were excluded if they were suspected of having difficulty opening their airways (Mallampati score of III–IV, or a mouth opening of <2.5 cm). Patients were also excluded if they had a history of upper respiratory tract infection in the past two weeks, serious cardiovascular disease, gastroesophageal reflux disease (GERD), or a body mass index ≥ 30 kg/m^2.

The patients were not given premedication. On arrival to the operating room, each patient was attached to routine monitors and Ringer's lactate solution (10 ml/kg) was infused over 20 min and then maintained at a rate of 100 ml/h. Following the initial fluid bolus, patients were infused with dexmedetomidine (Jiangsu Hengrui Medicine Co., Ltd., China) at 1.0 μg/kg over 10 min. The target-controlled infusion of propofol (AstraZeneca, Italy) was then started. The LMA "Supreme" (The Laryngeal Mask Company, Ltd., Singapore) was inserted when the infusion and target-controlled infusion concentrations reached equilibrium at the adjusted concentration, and the BIS value was 40–50. A size 3 LMA was selected for patients weighing 30–50 kg, a size 4 LMA was used for patients weighing 50–70 kg, and a size 5 LMA was used for patients weighing >70 kg. Target-controlled infusion (TCI) anesthesia with propofol was administered using a Graseby 3500 target-controlled infusion pump (Smiths Medical, USA). The target concentration of propofol was adjusted according to Dixon's up-and-down sequential method (Kim et al., 2008; Lu et al., 2003). The first patient's initial target-controlled infusion concentration of propofol was 3.0 μg/ml. The target-controlled infusion effect-site concentration of propofol for subsequent patients was based on the previous patient's response to insertion of the laryngeal mask. If the insertion was successful, for the next patient, the target-controlled infusion concentration of propofol was decreased by 0.2 μg/ml. If the placement failed, the target-controlled infusion concentration of propofol was increased by 0.2 μg/ml.

The following variables were observed and recorded:

1. Response to LMA insertion: cough, holding of breath, laryngospasm, or conscious movement of the whole body were considered as a positive response (Yu et al., 2006).
2. Ease of LMA insertion was graded as follows: 1. Insertion without resistance, 2. mild resistance, 3. more resistance but mouth opened, and 4. resistance required additional doses of propofol for LMA insertion. Grades 1 and 2 were considered successful, while grades 3 and 4 were defined as failure of LMA insertion.
3. MAP, heart rate (HR), SpO_2, P_{ET} CO_2, and BIS values were recorded before anesthesia (T0), after dexmedetomidine infusion (T1), when the plasma concentration and effect-site concentration of propofol reached a balance at the set level (T2), and 1 min after LMA insertion (T3).
4. Induction time from the start of anesthesia until LMA insertion.
5. Adverse effects: hypotension, bradycardia, and apnea. Hypotension was defined as mean arterial pressure <60 mmHg or a decrease of more than 30% from baseline values for 1 min. Bradycardia was defined as having a HR below 50 beats/min or the HR decreased more than 30% from the baseline value for 1 min. Apnea was defined as P_{ET} CO_2 = 0 mmHg and RR = 0 breaths/min for more than 1 min. In cases of apnea, assisted ventilation was performed. Bradycardia was defined as a HR below 50 beats/min or the HR decreased by more than 30% from the baseline value for 1 min. In cases of bradycardia, 0.5 mg of atropine was administered. Hypotension was defined as a mean arterial pressure <60 mmHg. In cases of hypotension, 1–2 mg of dopamine was administered.

Patient data were reported as the mean ± standard deviation (SD). Statistical analysis was performed using the SPSS package (SPSS 12.0 for windows, SPSS Inc., Chicago, IL, USA). According to Dixon's up-and-down method (Dixon and Massey, 1983), the study continued until six pairs of successful and failed LMA insertions occurred. The 50% target concentration (EC50) of propofol for LMA insertion was defined as the mean of the median cross-over dose. The data were also subjected to probit regression analysis using the 95% effective target concentration (EC95) and the 95% confidence interval (CI). A P-value less than 0.05 was used to define the level of statistical significance.

RESULTS

All the cases were performed in the First Hospital of Jilin University from October 2011 to January 2012. The patients' ages ranged from 20 to 60 years old. They had an average height ± SD of 159.95 ± 3.69 cm and an average weight ± SD of 61.85 ± 8.54 kg. The average induction time, including the infusion time of dexmedetomidine and propofol, was 13.25 ± 0.68 min. The study was performed on 20 patients, and all patient data were included in the analysis.

The laryngeal mask was inserted without difficulty in 12 patients (60.0%), whereas insertion was difficult in 8 cases (40%). During laryngeal mask insertion, SpO_2 and $PETCO_2$ values did not change significantly compared to before insertion. In addition, postoperative follow-up found that patients had no intraoperative awareness.

The effect-site propofol concentration for successful LMA insertion in 50% of the patients with pre-injection of dexmedetomidine (EC50) was 2.351 μg/ml (1.737–2.6 μg/ml), while the EC95 was 2.854 μg/ml (2.588–2.944 μg/ml). Figure 1 shows the up-down diagram of the effect-site plasma concentration of propofol for all patients. Table 1 lists the changes in hemodynamic variables from the preoperative values after dexmedetomidine infusion, showing that the HR was significantly reduced after dexmedetomidine infusion.

DISCUSSION

The main finding in the present study was that pre-injection of dexmedetomidine can reduce the target-controlled plasma concentration of propofol required for LMA insertion. In addition, experimental application of a modified Dixon's up-and-down method was applied as this procedure is applicable to small clinical samples and has been widely used for calculating the EC_{50} values of a variety of drugs (Lu et al., 2003; Yu et al., 2006. In order to determine the EC_{50}, the modified Dixon's up-and-down method requires more than six inflection points (Dixon

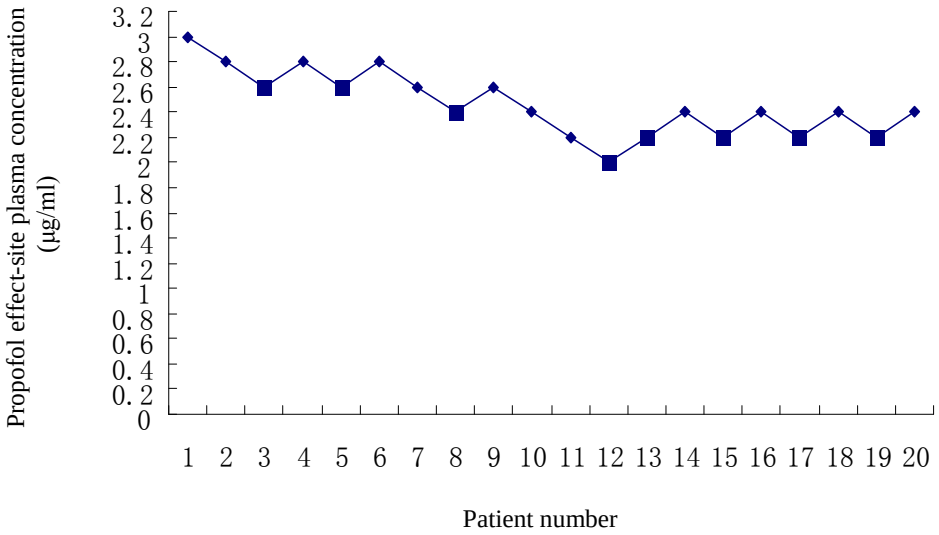

Figure 1. Target-controlled concentration of propofol for sequential patients. ◆,Indicates successful laryngeal mask insertion; ■, indicates failed laryngeal mask placement.

Table 1. Changes in hemodynamic variables at different observation times.

Time	HR (beats/min)	*P*-value	MAP (mmHg)	*P*-value
T0	80.15±14.57		94.22±14.09	
T1	65.45±9.37	0.001	93.41±13.46	0.865
T2	66.10±8.43	0.818	85.91±12.53	0.080
T3	64.8±7.38	0.725	86.76±14.75	0.267

MAP and HR values were recorded before anesthesia (T0), after dexmedetomidine infusion (T1), when the plasma concentration and effect-site concentration of propofol reached a balance at the set level (T2), and 1 min after LMA insertion (T3). P values represent the comparison to T0

and Massey, 1983).

Dexmedetomidine is a highly selective α_2 adrenergic receptor agonist. This drug was chosen because it can reduce the doses of opioids and sedatives (Li et al., 2007), and it can inhibit the stress response to intubation. Another significant advantage of dexmedetomidine is that it keeps the wake-up status of sedated patients with almost no inhibitory effect on respiration (Khan et al., 1999) The hemodynamic effects of dexmedetomidine depend on its dosage and injection speed (Li et al., 2007). A rapid intravenous infusion loading dose of l.0 μg/kg dexmedetomidine can cause short-term high blood pressure and a reflex decrease in HR. This reaction is more pronounced in a young, healthy population due to direct activation of α_2 receptors in the vascular smooth muscle, leading to vasoconstriction (Pandharipande et al., 2006). Dexmedetomidine at an intravenous infusion loading dose of 1.0 μg/kg/10 min can attenuate a hypertensive reaction. After a subsequent continuous infusion phase, dexmedetomidine has a central anti-sympathetic role and causes increased vagal activity, while blood pressure and HR can be moderately decreased (Triltsch et al., 2002). Dexmedetomidine-induced hypotension and bradycardia can be corrected by rehydration and by using drugs such as ephedrine and atropine. However, in the presence of hypovolemia or heart block, dexmedetomidine can cause serious consequences (Wang and Cheng, 2010).

Propofol is a short-acting intravenous anesthetic, a perfect sedative with a short half-life, but its analgesic effect is weak. Increasing the dose causes dose-dependent respiratory and circulatory suppression. It reduces the laryngeal responses and is widely used in laryngeal mask placement (Wysowski and Pollock, 2006). It has been reported that the ED50 of propofol was 2.99 μg/ml (95% CI 2.85–3.12 μg/ml) for smooth laryngeal mask placement when the anesthetic contained 1.5 μg/kg fentanyl (Yu et al., 2006). Clinical trials have shown that propofol alone (2.5–3 mg/kg) cannot meet the throat mask airway placement conditions; therefore, anesthesia is often combined with opioids (Park et al., 2007). Anesthesia induction with propofol alone requires higher doses with consequent fluctuations in hemodynamics and respiratory depression.

In this study, infusion of dexmedetomidine at 1.0 μg/kg/10 min before propofol induction of anesthesia

could reduce the effect-site concentration of propofol, reduce the amount used, and in turn reduce the cardio-vascular responses. Dexmedetomidine also maintains normal breathing; therefore, small doses of dexmedetomidine can be used as an adjuvant in general anesthesia, especially during induction and difficult airway insertion to maintain the awake status and spontaneous breathing while patients are sedated.

In conclusion, dexmedetomidine combined with target-controlled infusion of propofol can be used for LMA placement, with few adverse reactions. In addition, dexmedetomidine sedation can effectively reduce the target-controlled plasma concentration of propofol.

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ABBREVIATIONS

LMA, Laryngeal mask airway; **TCI,** target-controlled infusion; **HR,** heart rate.

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