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Original Article

Male requires a higher median target effect-site concentration of propofol for I-gel placement when combined with dexmedetomidine☆

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ABSTRACT

Objective: The supraglottic airway device (SAD) can be used for airway management of spontaneous breathing patients, and propofol is commonly applied for the SAD placement. This study was designed to assess the effect of gender on median target effect-site concentration (Ce_{50}) of propofol for I-gel placement when combined with dexmedetomidine.
Material and method: 19 males and 18 females, aged 18 to 59 and undergoing elective surgery, were enrolled. After intravenous infusion of dexmedetomidine 1.0 μg/kg over 10 min followed by continuous infusion of 0.4 μg/kg/h, target-controlled infusion of propofol under Marsh model was started and the initial Ce of propofol was set at 4.79 μg/mL and 4.35 μg/mL in the male and female patients, respectively. The I-gel was inserted when the Ce of propofol reached the pre-set concentration and bispectral index value was less than 60. The Ce of propofol required for I-gel placement was determined by the Dixon up-and-down method.
Results: The Ce_{50} (95% confidence interval) of propofol required for I-gel placement were 4.082 μg/mL (3.798–4.332 μg/mL) and 3.509 μg/mL (3.266–3.749 μg/mL) in male and female patients, respectively, with a significantly higher Ce_{50} in males.
Conclusion: When combined with dexmedetomidine, males compared with female require a higher Ce_{50} of propofol for I-gel placement compared to females.

1. Introduction

The supraglottic airway device (SAD) can be well tolerated by patients and is often used for airway management of spontaneously breathing patients undergoing a short surgical procedure. However, SAD placement needs a sufficient depth of anaesthesia so as to avoid the adverse responses of the upper airway. Propofol used for anaesthesia induction can inhibit the responses by SAD placement [1–3], but it is often of poor effect when on its own [4], or has an excessive dosage requirement [5,6], and even causes respiratory depression [7,8]. Furthermore, the common combination of propofol and opioid drugs can also induce respiratory depression. Given the little respiratory depression effect [9], dexmedetomidine is often used as sedative adjuvant for patients who are required to maintain spontaneous breathing during surgery [10], and has been combined with propofol for SAD placement [11]. It has been shown that dexmedetomidine may reduce the dose of propofol [12]. In addition, there is a growing body of evidence that gender may significantly change the pharmacokinetics and pharmacodynamics of propofol [13–15], and is an independent factor affecting the responses of the patient to general anaesthesia [16,17]; namely, female patients are less sensitive to the hypnotic effect of propofol [18] and are faster to recover from general anaesthesia [15,18–21]. To our knowledge, however, there has been no study to assess the effect of gender on the effective dose of propofol required for SAD placement. Thus, this study was designed to determine whether there was significant difference between female and male patients in the median effective target effect-site concentration (Ce_{50}) of propofol required for I-gel placement when combined with dexmedetomidine.

2. Materials and methods

The study was approved by the Clinical Research Ethics Committee of our hospital and registered in chictr.org (Registration number: ChiCTR-OCH-14004897). Patients, aged 18 to 59,

☆ Gender and Ce_{50} of propofol for I-gel placement.
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body mass index (BMI) 18.5–24.0 kg/m^2, undergoing lower limb surgery under general anaesthesia and nerve block with spontaneous breathing in our hospital, were enrolled in this study. All the participants were American Society of Anaesthesiologists physical status classification 1 or 2, Mallampati grade 1 or 2, and had a mouth opening of more than 2.5 cm. Patients were excluded if they had one of the following criteria: history of hypertension, gastroesophageal reflux disease, pathology of oral cavity and pharynx, taking sedatives or opioid drugs over the last two weeks, bradycardia or cardiac conduction block, abnormal liver or kidney function. Furthermore, none of the female patients included in the study was on her period. All subjects gave the informed consent for the tests, and this study was conducted in adherence to the Declaration of Helsinki and the principles of our Hospital Clinical Research Ethics Committee.

The patients were premedicated with an intramuscular injection of penehyclidine hydrochloride 0.01–0.02 mg/kg. After arriving in the operating theatre, standard monitoring, including electrocardiography, non-invasive arterial pressure and pulse oximetry was established. An 18-G venous catheter was placed, and lactated Ringer's injection was infused at a rate of 15 mL/kg/h. The bispectral index (BIS) electrodes were placed on the patient's forehead for monitoring the depth of anaesthesia using a VISTA BIS monitor (Aspect Medical Systems, USA).

Before the target-controlled infusion of propofol, dexmedetomidine (Batch No: 1312031, Guorui Pharmaceutical Co., Ltd, Leshan, China) 1.0 μg/kg was intravenously infused within a 10-min period. Thereafter, dexmedetomidine was continuously infused at a rate of 0.4 μg/kg/h and target-controlled infusion of propofol (Batch No: KN141, AstraZeneca, UK) under Marsh model using a CP-700 TCI pump (Slgo medical technology co., LTD, Beijing) was initiated for anaesthesia induction.

The median effective target effect-site concentration (Ce_{50}) of propofol required for I-gel placement was determined by the

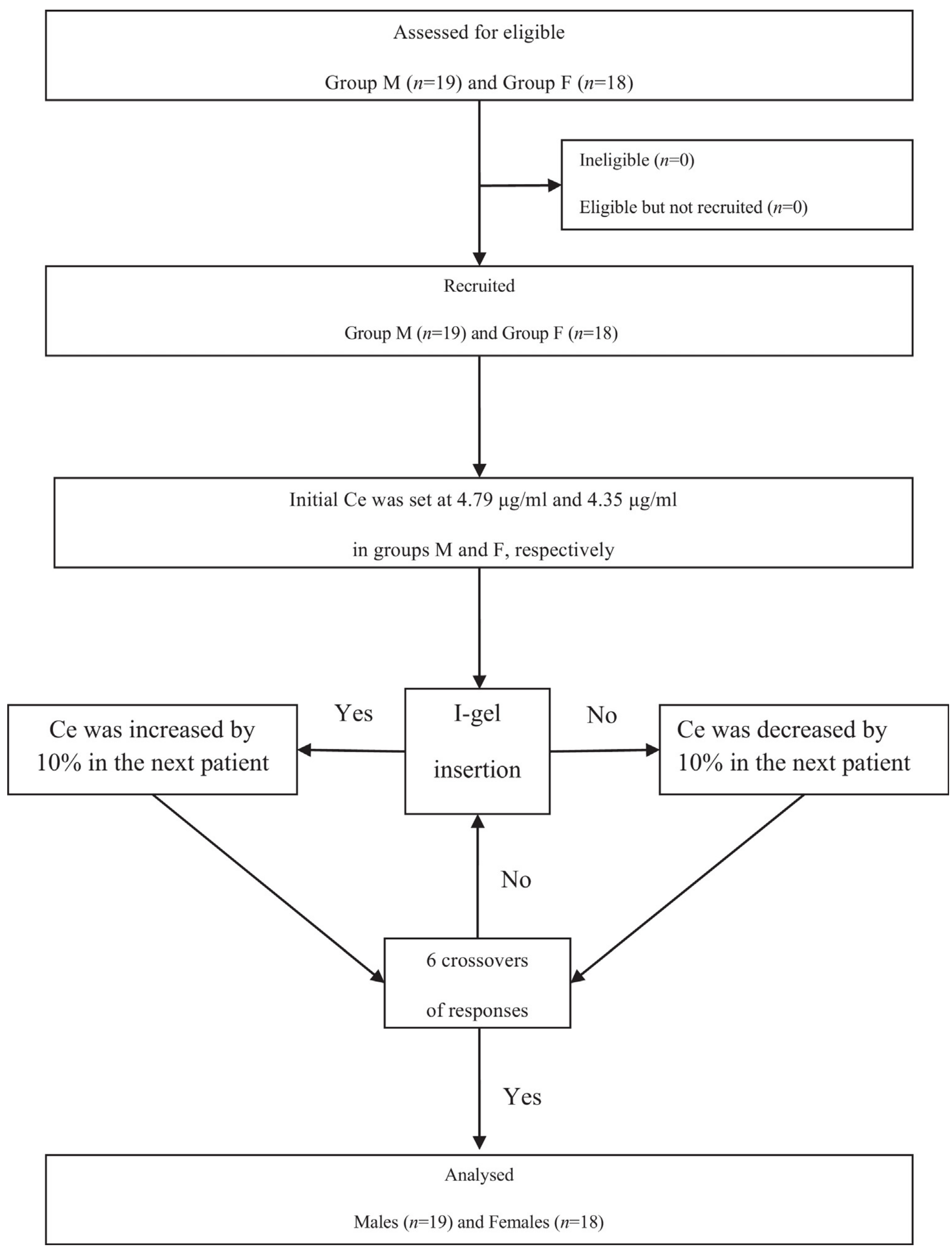

Fig. 1. Flow chart for the Dixon's up-and-down method.

Dixon's up-and-down method [22]. In our preliminary experiment including 20 males and 20 females, the inhibition rate of the responses by the I-gel placement reached 95% when the initial Ce of propofol was set at 4.79 and 4.35 μg/mL in male and female patients, respectively, when combined with the above dexmedetomidine dose regimen. Thus, the initial Ce of propofol used in male and female patients were 4.79 and 4.35 μg/mL, respectively. According to the occurrence or no occurrence of the responses of the previous patient to I-gel placement, the Ce of propofol was increased or decreased by 10% in the next patient (Fig. 1).

When the pre-set Ce of propofol was reached and BIS value was less than 60, the I-gel (Intersurgical Co., Ltd, UK) was inserted using the rotational technique [23]. The size of I-gel was selected based on the body weight of the patients (size 3 for 30 kg ≤ body weight ≤ 60 kg, size 4 for 60 kg < body weight ≤ 90 kg and size 5 for body weight > 90 kg) according to the manufacturer's specifications. If the patient's response was too strong and I-gel placement failed, additional propofol 2 mg/kg was intravenously injected before another placement attempt.

All I-gel placements were performed by an experienced anaesthesiologist. A 3-point, six-category scale (a–f) [24] was used to grade the insertion conditions of I-gel: a. Resistance to mouth opening grading: no, significant, or undue force required; b. Resistance to insertion grading: no, significant, or undue force required; c. Swallowing grading: nil, slight, or gross; d. Coughing and gagging grading: nil, slight, or gross; e. Head or body movement grading: nil, slight, or gross; f. Laryngospasm grading: nil, partial, or total. Laryngospasm was defined as prolonged obstruction with a correctly placed I-gel. A total score for insertion conditions was calculated by adding up the swallowing, gagging, movement, and laryngospasm grades (1, 2, or 3). Mouth opening and ease of insertion were excluded because they were significantly influenced by anatomical features of the upper airway [25]. A score of 4 was considered as an optimal condition for I-gel placement [24].

If respiratory depression occurred during this study, mask ventilation or assisted ventilation through I-gel was performed. If heart rate was less than 50 beats/min or more than 100 beats/min, atropine 10 μg/kg and esmolol 0.25 mg/kg were intravenously administered, respectively. If increase or decrease in mean artery pressure was more than 30% of the baseline value, phenylephrine 1 μg/kg and nicardipine 4 μg/kg were intravenously administered, respectively.

3. Statistical analysis

According to the requirement of the Dixon's up-and-down method, at least six crossovers (successive "accept" and "refuse" appear) are needed to determine ED_{50} value of a drug [22]. Considering that the previous case to the first appearance of I-gel insertion responses as the first selected case, the trial was ended after six consecutive pairs were achieved (Fig. 2).

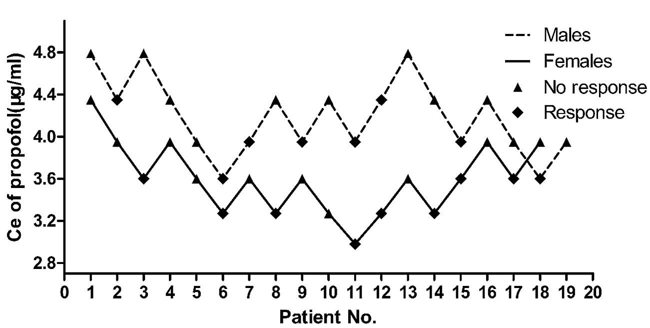

Fig. 2. Response of studied patients to different Ce of propofol.

Data with a normal distribution were expressed as mean ± standard deviation. Statistical comparisons of parametric data between groups were carried out using a Student's paired *t* test. Statistical comparisons of nonparametric data between groups were executed with a χ^2 test. The ED_{50} (95% confidence interval) and ED_{95} (95% confidence interval) of propofol in male and female patients were analysed by the probit regression. A U test was used to compare the difference in the Ce_{50} values between groups. The criterion for rejection of the null hypothesis was $P < 0.05$ for all tests. Statistical analysis of all data was completed with SPSS (Version 13.0, SPSS, Inc., Chicago, IL, USA). The dose-response curves were plotted using the GraphPad Prism 5.0 (GraphPad Software, Inc., USA).

4. Results

A total of 19 males and 18 females were enrolled in this study (Fig. 1), and patients' demographic characteristics were presented in Table 1. The male and female patients were comparable in terms of age, BMI, ASA physical status classification, Mallampati class and mouth opening. The respiratory depression, bradycardia, tachycardia, and significant blood pressure fluctuations during the study were not significantly different between male and female patients (Table 2). No patient received the additional bolus of propofol due to the strong response and failed I-gel placement.

The dose-response curves of propofol in male and female patients are shown in Fig. 3. The Ce_{50} (95% confidence interval) of propofol required for I-gel placement were 4.082 μg/mL (3.798–4.332 μg/mL) and 3.509 μg/mL (3.266–3.749 μg/mL) in male and female patients, respectively, with a significant higher Ce_{50} in males ($P = 0.017$). The Ce_{95} (95% confidence interval) of propofol required for I-gel placement were 4.638 μg/mL (4.361–5.649 μg/mL) and 3.987 μg/mL (3.736–4.906 μg/mL) in male and female patients, without significant difference ($P = 0.223$).

5. Discussion

The Dixon's up-and-down method is easy to use to dermine the median effective dose or concentration of a drug, because it can not only make full use of the data information, but also reduce the tested cases by more than 30%, and obtain accurate results [26]. As to the previous work by Patel et al. [27], in designing this study, a loading infusion of dexmedetomidine 1.0 μg/kg over 10 min followed by continuous infusion of 0.4 μg/kg/h was used. Based on the results of our preliminary experiment, the initial Ce of

Table 1
Demographic characteristics of patients.

	Males (*n* = 19)	Females (*n* = 18)	*P*-value
Age (yr)	42.4 ± 8.5	41.8 ± 8.3	0.8295
BMI (kg/m2)	22.7 ± 2.1	21.8 ± 3.2	0.3136
ASA I/II	12/7	12/6	1.0000
Mallampati I/II	16/3	14/4	0.6928
Mouth opening (cm)	3.8 ± 0.4	3.6 ± 0.5	0.2424

Data are presented as mean ± standard deviation or numbers. BMI: Body mass index; ASA: American Society of Anesthesiologists physical status.

Table 2
The occurrence of adverse reactions during study.

	Males (*n* = 19)	Females (*n* = 18)	*P*-value
Respiratory depression	2	3	0.6599
Bradycardia	1	2	0.6039
Tachycardia	2	1	1.0000
Significant blood pressure fluctuation	0	1	0.4865

Data are presented as numbers.

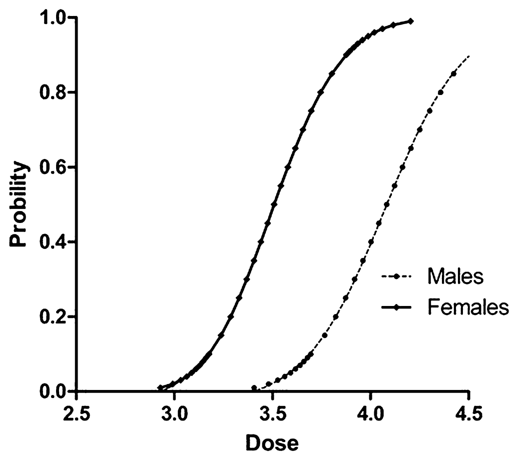

Fig. 3. Dose–response curves of propofol for I-gel placement in males and females.

propofol was set at 4.79 and 4.35 μg/mL in male and female patients, respectively. In this study, moreover, the Ce of propofol by a geometric form was used, the ratio between the two adjacent propofol concentrations was 1.1, and the six consecutive pairs were achieved. In this way, the error caused by individual differences can be minimised and the impact of the initial dose on the results can be avoided [16], ensuring the objectivity of our results. In addition, in order to avoid the potential impact of liver or kidney dysfunction on the Ce_{50} of propofol required for I-gel placement, all the subjects enrolled in this study have normal liver and kidney functions.

Our study showed that the Ce_{50} of propofol required for I-gel placement were 3.266–4.332 μg/mL, which seem to be lower that the findings of previous studies [5,6]. Richebé et al. [5] showed that the Ce of propofol required for successful placement of the laryngeal mask airway is 7.3 ± 0.2 μg/mL. In the study by Taylor and Kenny [6], moreover, 14 of 15 patients using a Ce of propofol 6 μg/mL obtained a successful placement of the laryngeal mask airway within 3 min, and all 15 patients using a Ce of propofol 7 μg/mL obtained a successful placement of the laryngeal mask airway within 3 min. One possible reason for the differences between previous results and ours may be attributable to combined use of dexmedetomidine in this study. It has been shown that dexmedetomidine can reduce the dosage of propofol for the BIS-guided closed-loop anaesthesia [12]. As no study has compared the responses by placement of different SADs, moreover, it is also unclear whether use of different SADs is contributed to the differences in the Ce of propofol between our and previous studies.

Our study also showed that Ce_{50} of propofol required for I-gel placement was significantly larger in males than in females. That is, males were less sensitive to propofol than females, which is contrary to the findings of most previous studies. For example, females have been shown to be less sensitive to hypnotic effect of propofol [18] and recover faster from general anaesthesia than males [15,18–21]. Furthermore, females require more propofol for loss of consciousness and maintenance of anaesthesia than males [28,29]. In previous studies, gender-related difference in pharmacodynamics of propofol has been contributed to different hormone levels between male and female patients, which may cause propofol metabolic differences [30]. Furthermore, neurosteroids and sex hormones such as pregnanolone have sedative and anaesthetic effects [31–33]. The available literatures indicate that in the luteal phase of menstrual cycle [34] and pregnancy [35,36], the increase in the production of progesterone can decrease anaesthetic requirements. Fu et al. [37] show that patients in the luteal phase of the menstrual cycle have a lower EC_{50} of propofol for loss of consciousness and a shorter emergence time compared with those in the follicular phase. Differences in progesterone levels between menstrual phases may contribute to these anaesthetic effects. In addition, there are sex differences in the pharmacokinetics of propofol [13–15]. It has been documented that females have a higher clearance of propofol and a higher distribution volume compared with males [38–40]. Differences in the pharmacokinetics of propofol between genders may also contribute to less anaesthetic effect of propofol in females. However, our findings are consistent with the results of another study, in which N_2O decreases more propofol in females than in males at the same depth of anaesthesia [41].

The detailed reasons that our finding is contrary to the results of most previous studies are not clear. According to the available literatures, we speculated that this inconsistent finding may be attributable to the following aspects. First, as gender can affect the clinical effectiveness of opioids and muscle relaxants [42], the clinical sedative efficiency of dexmedetomidine may have a gender-related difference. Second, the inhibition of airway responses by anaesthetics has been demonstrated to have a gender-related difference, as this inhibition is one of the most important aspects of achieving successful supraglottic airway placement without a neuromuscular blocking agent that is different from sedation [18,43,44]. A previous study on the remifentanil requirements for cough suppression during emergence showed that an antitussive effect was achieved at a higher remifentanil concentration in male patients, as compared with female patients [43]. It seems that the anaesthetic concentrations required for cough suppression may differ based on gender under similar clinical conditions. It has also been shown that male sex hormones might promote reflex airway responsiveness and that a gender disparity exists in terms of airway responsiveness to cholinergic stimulation [44]. Lastly, when combined with propofol and dexmedetomidine, the interaction between them might change with gender-related sensitivity to propofol. The pharmacodynamic interaction between propofol and dexmedetomidine and its dependence on gender needs clarification in future studies.

Some limitations of this study must be emphasised. This is a prospective study; however, it was not conducted using a double-blind design, as the anaesthesiologist who placed the I-gel was aware of the group assignments. The observer was blinded to the different propofol Ce, but information pertaining to a previous patient might have affected the decision regarding I-gel placement for the next patient. Randomisation seemed difficult to perform in this study; on the one hand, individuals were grouped by gender, and on the other hand, the Ce of propofol used for a patient was based on whether the prior patient responded. Secondly, the female patients included in this study were not in the same ovarian phase, and the plasma sex hormones levels were not detected in the two groups. Thus, it was unclear whether differences in the plasma sex hormones levels between male and female patients would have been attributable to our results. These issues deserve the further studies.

In conclusion, this study demonstrates that when combined with dexmedetomidine, males compared with females require a higher Ce_{50} of propofol for I-gel placement.

Authors' contributions

Ming-Ming Han significantly contributed to design and implement of study, acquisition, analysis and interpretation of data, and drafted the manuscript. Fang Kang and Xiang Huang substantially participated to acquisition and interpretation of data. Fu-Shan Xue and Juan Li considerably contributed to conception and design of study, helped to draft the manuscript and revised it critically. All authors had seen and approved the final manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

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