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ORIGINAL ARTICLE

A randomized controlled trial of the effect of preoperative dexmedetomidine on the half maximal effective concentration of propofol for successful i-gel insertion without muscle relaxants

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Abstract
Background Dexmedetomidine is a useful anesthetic adjuvant for general anesthesia. We determined whether preoperative dexmedetomidine administration could reduce the half maximal effective concentration (EC_{50}) of propofol for successful i-gel insertion without muscle relaxants.
Methods Thirty-seven patients were randomly allocated to one of two groups. In the dexmedetomidine group ($n = 19$), dexmedetomidine (1 μg/kg) was loaded for 10 min preoperatively. In the control group ($n = 20$), the same volume of 0.9 % normal saline was administered in the same manner. The EC_{50} of propofol for successful i-gel insertion was determined using Dixon's up-and-down method. The EC_{50} of propofol was calculated as the mid-point concentration after at least six crossover points had been obtained. For successful i-gel insertion, all of the following four factors were required—(1) no major movement of the body within 1 min of insertion, (2) no significant resistance to mouth opening, (3) cough ≤2, and (4) visible square wave capnogram without air leakage at a peak airway pressure of <10 cmH_2O. Mean blood pressure (MBP) and heart rate (HR) were monitored during the peri-insertion period of i-gel.
Results The EC_{50} of propofol for successful i-gel insertion was 3.18 μg/mL in the dexmedetomidine group and 6.75 μg/mL in the control group ($p < 0.001$). The incidence of hypotension (MBP <80 % of the baseline) during the peri-insertion period of i-gel was higher in the control group ($p = 0.001$), whereas the incidence of bradycardia (HR <80 % of the baseline) was higher in the dexmedetomidine group ($p = 0.001$).
Conclusions Preoperative dexmedetomidine reduced the EC_{50} of propofol for successful i-gel insertion without muscle relaxants.

Keywords Dexmedetomidine · i-gel · Propofol

Introduction

The i-gel (Intersurgical Ltd., Wokingham, UK) is a non-reusable supraglottic airway device that has a unique advantage over laryngeal mask airway (LMA) devices with respect to insertion. Specifically, the i-gel has a soft, bulky, non-inflatable cuff. Therefore, an appropriate anatomic seal for the supraglottic airway can be accomplished without air inflation. The effectiveness of i-gel for airway management has been reported in patients with out-of-hospital cardiac arrest and in those with difficult airways in the operating room [1–6].

Propofol is a useful induction agent for supraglottic airway device insertion without muscle relaxants because it profoundly inhibits pharyngeal and laryngeal reactivity [7, 8]. A previous report showed that the effect-site concentration of propofol for successful classic LMA insertion in 50 % of adults (EC_{50}) without muscle relaxants in healthy

Trial Registration Identifier: NCT02097407 (http://www.clinicaltrials.gov).

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Table 1 The i-gel™ insertion conditions

Condition	Patient response
Excellent	Lack of movement of the body or limbs within 1 min of insertion, no cough or gagging, and good jaw relaxation
Good	Minor movement of the body, such as finger movement within 1 min of insertion, and good jaw relaxation and one or two coughs or gags
Difficult	Major movement of the body or limbs within 1 min of insertion or >2 coughs or gags, or severe resistance of mouth opening

Difficult i-gel insertion condition is considered as failure

male patients was 8.72 (0.55) μg mL^{-1} [9]. The EC_{50} of propofol may be dependent on the type of supraglottic airway device used. A previous study comparing the EC_{50} of the propofol concentration between classic and proseal LMA insertions demonstrated that the EC_{50} of propofol needed for Pro-Seal LMA insertion was 35 % greater than that needed for classic LMA insertion [10]. Unfortunately, no investigation has been performed to determine the EC_{50} of the propofol concentration required for i-gel insertion without muscle relaxants.

Dexmedetomidine (DEX), a highly selective alpha-2 agonist, has sympatholytic, sedative, and analgesic properties. Such beneficial characteristics make DEX a useful anesthetic adjuvant for general anesthesia. Many reports have revealed the beneficial effects of DEX in terms of reducing airway secretion, hemodynamic response to noxious stimuli such as endotracheal intubation, intraoperative anesthetic requirements, and postoperative analgesic demand [11–16]. A previous investigation showed that preoperative clonidine, an alpha-2 agonist, decreased the EC_{50} required for LMA insertion [9]. However, there is no study concerning the effect of preoperative DEX on the EC_{50} of propofol needed for successful i-gel insertion.

We hypothesised that preoperative DEX administration can reduce the propofol concentration required for i-gel insertion. We conducted this study to find the EC_{50} of propofol needed for successful i-gel insertion without muscle relaxants and to determine the effect of preoperative DEX administration on the EC_{50} of propofol.

Methods

Setting and study design

After obtaining approval from the Institutional Review Board (IRB) of Seoul National University Hospital (number H-1203-041-400) and written informed consent from patients, we prospectively enrolled 39 American Society of Anesthesiologist (ASA) physical status I–II patients who were aged 20–65 years and scheduled for general anesthesia for minor urologic surgery between May and August 2012. Patients with an allergy to alpha-2 adrenergic agonists or propofol, anticipated difficult airway (cervical spinal disease, Mallampati score of III or IV, a mouth opening of <2.5 cm, and/or body mass index of >30 kg/m), unstable teeth, bradycardia of <50 beats/min, heart block greater than first degree, severe cardiorespiratory dysfunction, and symptoms of upper respiratory infection were excluded. The protocol for this clinical trial was registered at ClinicalTrials.gov (NCT02097407).

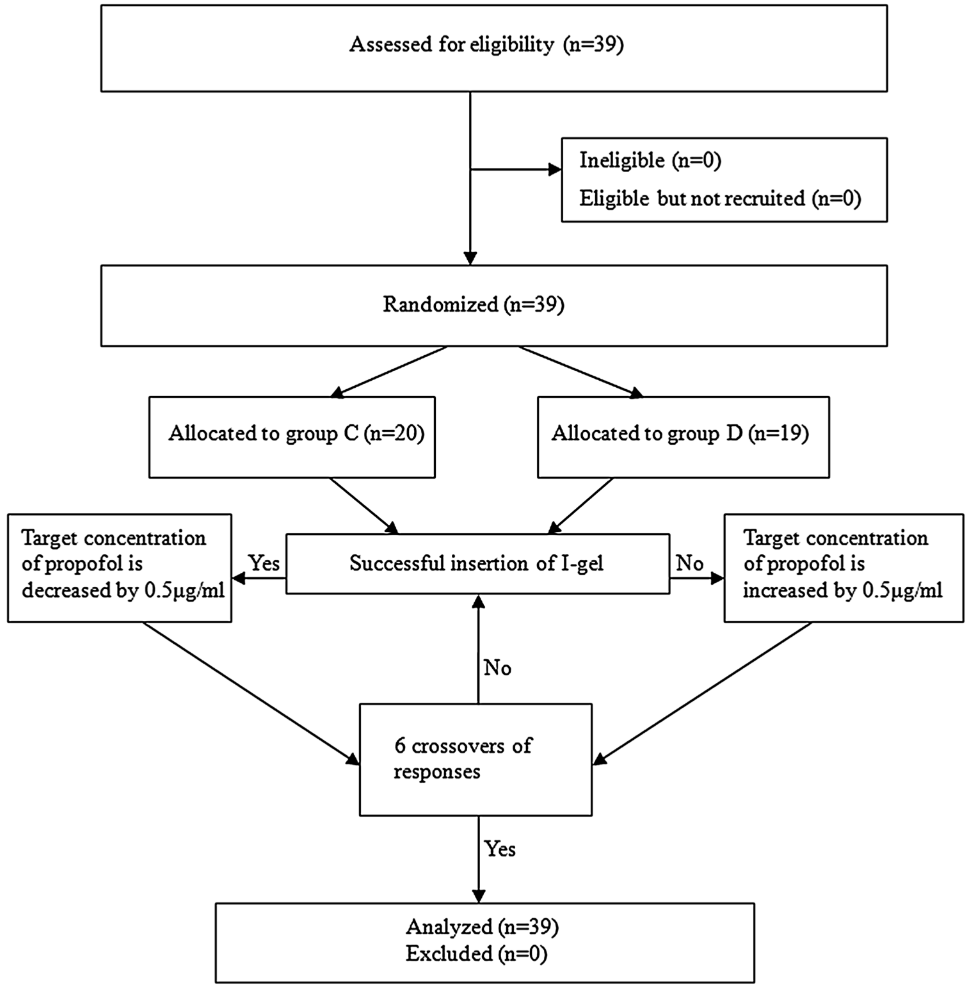
Group assignment

Patients were randomly allocated to one of two groups. Randomization was accomplished using random computer-generated numbers. The assignments were concealed in opaque envelopes and opened immediately before induction by a nurse who was blinded to this study and responsible for preparing the study drugs. In Group D, DEX (1 μg/kg) was intravenously loaded over 10 min before induction of anesthesia. In Group C, the same volume of 0.9 % normal saline was administered in the same manner.

Study protocol

All patients were pre-oxygenated with 100 % oxygen with spontaneous breathing for 3 min before the end of loading of DEX or normal saline. Anesthesia was induced with predetermined effect-site propofol concentrations using a target-controlled infusion device (Orchestra; Fresenius-Vial, Brezins, France). The first patient in Group C and D received an effect-site propofol concentration of 5 and 3 μg/mL, respectively. We used the Schnider pharmacokinetic model (k_{e0} = 0.46/min) for propofol [17]. After achieving equilibration of the plasma and effect-site propofol concentrations and confirming adequate anesthetic level, i-gel (size 4 for patients weighing 50–90 kg, size 3 for patients weighing 30–50 kg) was inserted using the standard technique by a single anesthesiologist staff member with expertise in i-gel insertion and who entered the operating room immediately before i-gel insertion to blind him to the group assignment. The i-gel insertion condition was classified by the anesthesiologist staff as excellent, good or difficult according to body movement, coughing, gagging, and jaw mobility (Table 1) [18]. If the patient shows an inadequate anesthetic level such

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



as a high BIS of >60 or intact eyelid reflex before i-gel insertion, it was regarded as 'failure', and additional propofol was administered to deepen the level of anesthesia. If we experienced difficult insertion conditions of the i-gel, it was also regarded as 'failure', and propofol was administered additionally after i-gel insertion. For 'successful' i-gel insertion, both of the following two factors are required—(1) excellent or good i-gel insertion condition and (2) visible movement of the chest and serial square wave capnograph trace without air leakage at a peak airway pressure of <10 cm H_2O [19]. Furthermore, the presence of laryngospasm and the number of external airway manipulations was noted.

The EC_{50} of propofol for successful i-gel insertion was determined by a modification of Dixon's up-and-down method [20–22]. A flow chart for the Dixon up-and-down method in this study is shown in Fig. 1. The response of each patient determined the effect-site propofol concentration for the next patient. If the response was deemed 'successful', the next target concentration of propofol was decreased by 0.5 μg/mL. If the response was deemed a 'failure', the target concentration was increased by the same dose. The process was repeated until at least the sixth crossover point (success/failure) was obtained.

After removing the i-gel, airway trauma (defined as any blood staining on the device) was noted by a junior anesthesiologist resident blinded to this study.

Measurements

The insertion time, defined as the time from picking up the i-gel until the initiation of mechanical ventilation, was recorded. The mean blood pressure (MBP), heart rate (HR), and bispectral index (BIS) were measured immediately before loading (baseline) and every 2 min for the 10-min DEX or normal saline loading, every 1 min during the 5-min anesthetic induction, and 1, 2, and 3 min after i-gel insertion. Hypertension was defined as an MBP >20 % higher than the baseline value, whereas hypotension was defined as an MBP >20 % lower than the baseline value. Tachycardia was defined as a HR >20 % higher than the baseline value, whereas bradycardia was defined as a HR >20 % lower than the baseline value.

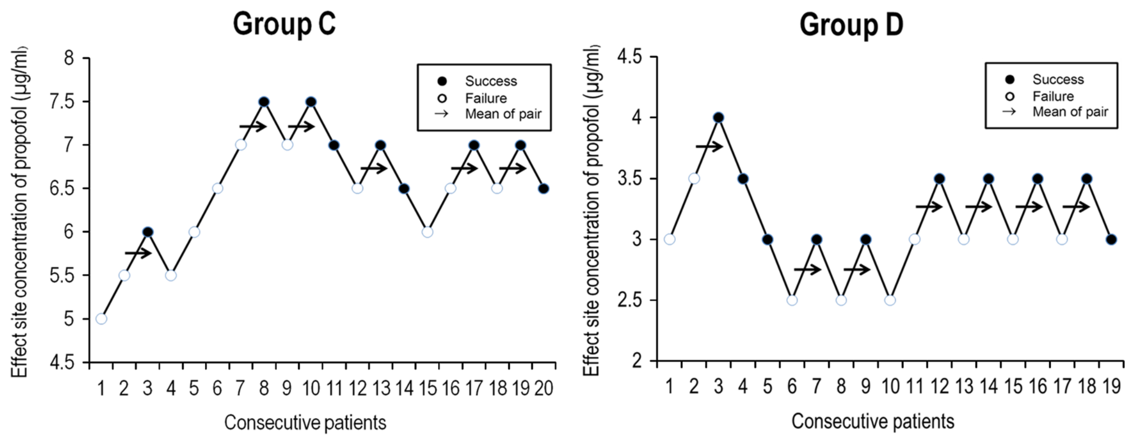


Fig. 2 Consecutive effect-site propofol concentrations for i-gel insertion in patients receiving preoperative dexmedetomidine (group D) or saline (group C)

Table 2 Patient characteristics

Variables	Group C ($n = 20$)	Group D ($n = 19$)	p-value
Male gender	15	18	0.182
Age (years)	41.2 (10.1)	36.1 (11.3)	0.146
BMI (kg/m^2)	24.1 (2.3)	25.0 (3.1)	0.328
ASA class (I/II)	17/3	17/2	1.000
Mallampati class (I/II)	16/4	15/4	1.000

Data are mean (SD) or number

Group C control group, *Group D* dexmedetomidine group

The primary measurement in this study was the EC_{50} of propofol required for successful i-gel insertion. The secondary measurement was the presence of airway trauma after i-gel insertion.

Statistics

Pace and Stylianou reported that 20–40 subjects are generally needed in the Dixon up-and-down method, but when the sixth crossover point (success/failure) is achieved, no further subject enrolment is required [23]. The EC_{50} of propofol was determined by calculating the mean of the midpoint concentration of all independent pairs of patients who manifested a crossover from a negative to a positive response (i.e., failure to success of insertion of i-gel) [20–22]. Probit analysis was used to calculate the 95 % confidence interval (CI) of the propofol EC_{50} and EC_{95} for successful i-gel insertion. The propofol EC_{50} and demographics were analysed by an independent t test. Hemodynamic data and BIS values were subjected to repeated-measures ANOVA. If the difference between the two groups was significant, an independent t test was used to determine the difference at each time point. The number of patients with blood-tinged i-gel, ASA class, hypotension, and bradycardia were analysed by chi-squared test or Fisher's exact test as appropriate. A p value of <0.05 was considered to indicate statistical significance.

Results

Thirty-nine patients were enrolled in this study. Two patients in Group D showed an inadequate anesthetic level such as a high BIS of >60, spontaneous movement, and an intact eyelid reflex before i-gel insertion. At least six pairs of success–failure crossovers were obtained in 19 and 20 patients in Groups D and C, respectively (Fig. 2).

Patient characteristics between Groups D and C were not significantly different (Table 2). There were no significant differences in the responses of individual patients to i-gel insertion between the two groups (Table 3). No patient in either group showed laryngospasm during i-gel insertion, external airway manipulation during i-gel insertion, or blood-tinged airway equipment after removing i-gel.

The EC_{50} of propofol for successful i-gel insertion, which was calculated from the modified Dixon up-and-down method, was 3.18 (0.35) µg/mL and 6.75 (0.55) µg/mL in Groups D and C, respectively ($p < 0.001$). The EC_{50} and EC_{95} of propofol for successful i-gel insertion, which were estimated from Probit analysis, were 3.01 µg/mL (95 % CI 2.57–3.51) and 3.70 µg/mL (95 % CI 3.37–7.14) in Group D and 6.75 µg/mL (95 % CI 6.17–8.02) and 7.78 µg/mL (95 % CI 7.17–16.14) in Group C, respectively.

Changes in MAP over time between the two groups differed markedly ($p < 0.05$, Fig. 3). MBP was significantly higher in Group D than in Group C from 4 min of propofol infusion until 3 min following i-gel insertion ($p < 0.01$). The number of patients with decreased MBP of >20 % of

Table 3 Data related to i-gel insertion

	Success ($n = 18$)			Failure ($n = 21$)		
	Group C ($n = 8$)	Group D ($n = 10$)	p-value	Group C ($n = 12$)	Group D ($n = 9$)	p-value
Jaw mobility						
Fully relaxed	6	8	1.000	5	7	0.251
Mild resistance	2	2		3	1	
Tight but open	0	0		4	1	
Closed	0	0		0	0	
Cough						
None	8	10	NM	8	7	0.722
1–2 coughs	0	0		1	1	
≥3 coughs	0	0		3	1	
Gag						
None	8	10	NM	6	5	1.000
Yes	0	0		6	4	
Body movement						
None	8	8	0.447	2	0	0.157
Minor	0	2		2	0	
Major	0	0		8	9	
Insertion time (s)	20.3 (4.4)	21.5 (4.1)	0.877	22.1 (5.8)	20.0 (5.6)	0.798
Other events						
Hypotension	8	3	0.004	7	0	0.007
Hypertension	0	1	1.000	0	6	0.002
Bradycardia	0	7	0.004	3	8	0.008
Tachycardia	1	2	1.000	6	1	0.159
Laryngospasm	0	0	NM	0	0	NM
Airway trauma	0	0	NM	0	0	NM

Data are number or mean (SD)

Group C control group, *Group D* dexmedetomidine group, *NM* not measurable

the baseline value was higher in Group C than in Group D [15 (75 %) vs 3 (16 %), $p = 0.001$, Table 2]. Changes in HR over time between the two groups were markedly different ($p < 0.01$, Fig. 3). HR was significantly lower in Group D than in Group C after 8 min of loading; this difference was maintained after i-gel insertion ($p < 0.01$). The number of patients with decreased HR of >20 % of the baseline value was lower in Group C than Group D [3 (15 %) vs 15 (79 %), respectively; $p < 0.001$, Table 2]. However, no patient showed hypotension (MBP <60 mmHg) or severe bradycardia (HR <40 beats/min) during the entire study period in either group. Changes in the BIS over time were not different between the two groups.

Discussion

This is the first study to determine the EC_{50} of the propofol concentration required for i-gel insertion without muscle relaxants in adult patients; we demonstrated that the EC_{50} of propofol for successful i-gel insertion was 6.75 μg/mL and that preoperative DEX administration reduced the EC_{50} of propofol by 53 %.

Different supraglottic airway devices can have different propofol concentrations of EC_{50} needed for their insertion. The EC_{50} of propofol required for successful insertion of classic LMA is 6.5–8.7 μg/mL [9, 24–26]. Interestingly, a previous study demonstrated that the EC_{50} of propofol needed for successful Pro-Seal LMA insertion was 38 % greater than that needed for successful classic LMA insertion [10]. Another report showed that the EC_{50} of propofol required for laryngeal tube insertion was 14 % lower than that required for classic LMA insertion [26]. Such findings suggest that the extent of airway reactivity can be affected by the shape and rigidity. In this study, the EC_{50} of propofol needed for successful i-gel insertion without muscle relaxants was 6.8 μg/mL. The i-gel has a unique noninflatable cuff that is bulkier than that of the classic or Pro-Seal LMA before inflation. The i-gel cuff is slightly harder than the inflatable LMA cuff. We believe that the i-gel cuff is the

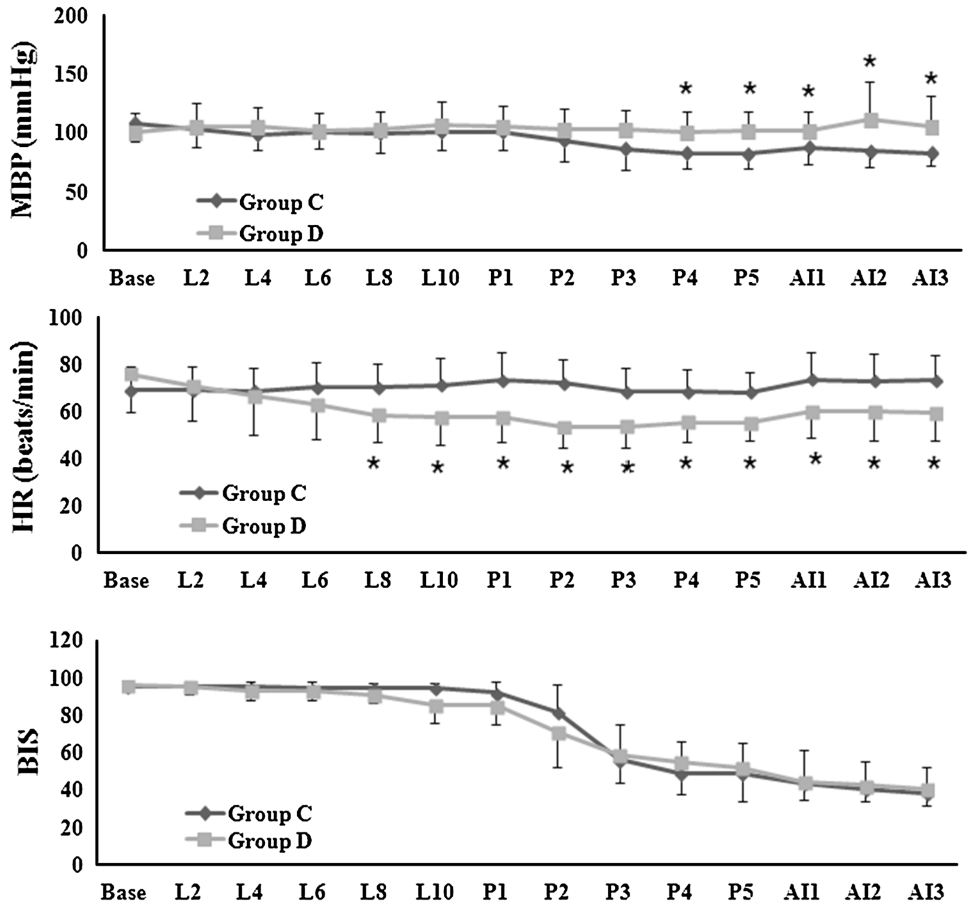


Fig. 3 BIS and hemodynamic variables. Base, *L*2, *L*4, *L*6, *L*8, and *L*10 indicate before loading and 2, 4, 6, 8, 10 min after loading of dexmedetomidine (group D) or saline (group C), respectively. *P*1, *P*2, *P*3, *P*4, *P*5 indicate 1, 2, 3, 4, 5 min after propofol infusion, respectively. *AI*1, *AI*2, *AI*3 indicate 1, 2, 3 min after i-gel insertion, respectively. *MBP* mean blood pressure, *HR* heart rate, *BIS* bispectral index. * $p < 0.01$ compared with control group

main factor responsible for the airway reactivity, which is a key factor in successful i-gel insertion.

DEX is also known to be effective in reducing airway and reflex response during intubation [12, 14–16] and extubation [27, 28]. In this study, the major obstacles to successful i-gel insertion were inadequate jaw relaxation and increased airway reactivity. The i-gel insertion conditions were comparable between the two groups, but preoperative DEX administration decreased the EC_{50} of propofol required for successful i-gel insertion by 53 %. Such findings suggest that DEX may increase jaw relaxation and reduce airway reactivity during i-gel insertion. Consistent with our result, a previous study demonstrated that preoperative oral clonidine at 5 μg/kg dramatically reduced the EC_{50} of propofol needed for LMA insertion in male patients [9]. Another report indicated that the extent of the reduction of the propofol concentration for LMA insertion was ~25 % with oral clonidine premedication at 5 μg/kg [29]. We believe that the sedative and analgesic properties of DEX help to decrease the EC_{50} of propofol for i-gel insertion without muscle relaxants.

In this study, the EC_{95} of propofol for successful i-gel insertion was 7.78 μg/mL when anesthesia was induced with only propofol. In clinical practice, such high-dose propofol administration is not routinely used for anesthetic induction because anesthetic induction with high-dose propofol is associated with increased episodes of hypotension [30]. This study showed that preoperative DEX decreased the incidence of hypotension during anesthetic induction and after i-gel insertion by reducing the high propofol concentrations required for anesthetic induction. In addition, because low-dose DEX decreases MBP and HR due to its sympatholytic effect [11, 31], preoperative DEX administration can blunt the sympathoadrenal responses to i-gel insertion. Therefore, it is reasonable to administrate DEX before anesthetic induction for hemodynamic stabilization during the peri-insertion period of i-gel.

In general, propofol is the first-choice induction agent when supraglottic airway devices are inserted without the use of muscle relaxants because it substantially reduces airway reactivity [7, 8]. Additionally, a previous study showed that propofol in combination with butorphanol provided absolute jaw relaxation and excellent LMA insertion conditions [32]. For this reason, propofol was used as an induction agent in this study. Muscle relaxants may be helpful in blocking body movements and reducing the cough and gag reflex caused by i-gel insertion. However, muscle relaxants are not always necessary for successful i-gel insertion.

Opioids may improve the i-gel insertion conditions by deepening the anesthetic level; however, they are associated with muscle rigidity, delayed anesthetic recovery, and postoperative apnea, especially after short general anesthesia [33–35].

High-dose DEX administration or rapid administration of DEX can lead to tachycardia and bradycardia because of sudden exogenous catecholamine release [36, 37]. DEX 0.5–1 μg/kg loading over 10–15 min and subsequent continuous infusion of 0.5–1.0 μg/kg/min is generally recommended during general anesthesia [38, 39]. However, preoperative single administration of DEX 0.5–1 μg/kg over 10 min without continuous infusion is also a simple, easy, and effective adjuvant for general anesthesia [40, 41]. Previous studies on intubation-related hemodynamic response showed that preanesthetic single administration of DEX 1 μg/kg over 10–15 min effectively blunted an increase in MBP and HR after laryngoscopic intubation [15, 42, 43]. Therefore, in this study, DEX of 1 μg/kg was preoperatively administered over 10 min.

There were several limitations to this study. First, patients with normal airways were mainly included in this study. Therefore, the propofol concentration required for successful i-gel insertion was not investigated in patients with difficult airways or risk factors for i-gel insertion failure. A recent study identified male sex, old age, poor dentition, and impaired mandibular subluxation as risk factors for i-gel insertion failure [44]. Second, the propofol EC_{95} rather than the propofol EC_{50} for successful i-gel insertion is of clinical interest. A caution is needed in interpreting our results, especially the propofol EC_{95} because the value is estimated from Probit analysis, not measured directly. Third, initial effect-site propofol concentration was different between two groups in this study. Furthermore, the propofol concentration was never overlapped in either group during the study period. Therefore, although there was an effort to blind the investigator to the group assignment, this study was not thoroughly double-blinded, which may cause a bias. Finally, although opioids are commonly used during anesthetic induction, the effect of opioids used during anesthetic induction on the propofol EC_{50} for successful i-gel insertion was not investigated in this study because we focused on the effect of preoperative DEX on the propofol EC_{50} for successful i-gel insertion. A previous report indicated that remifentanil significantly reduced the EC_{50} of propofol required for successful insertion of supraglottic airway devices [18].

In conclusion, this investigation demonstrated that the EC_{50} of propofol required for successful i-gel insertion without muscle relaxants was 6.75 μg/mL and that preoperative DEX administration reduced the EC_{50} of propofol significantly.

Conflict of interest None.

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