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REPORTS OF ORIGINAL INVESTIGATIONS

Effective bolus dose of remimazolam for i-gel® insertion in nonparalyzed patients: a dose-finding study

Dose efficace en bolus de remimazolam pour l'insertion de l'i-gel® chez la patientèle non paralysée : une étude de détermination de dose

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Abstract

Purpose *Remimazolam is a recently developed ultra-short-acting benzodiazepine used for anesthesia induction and maintenance. Nevertheless, the effective bolus dose of remimazolam for i-gel® (Intersurgical Ltd., Wokingham, Berkshire, UK) insertion without the use of neuromuscular blocking agents (NMBAs) has not been well established.*

Methods *This study included 25 adult patients scheduled for surgery under general anesthesia who were eligible for i-gel use. Anesthesia was induced with predetermined bolus doses of remimazolam, starting at 0.3 mg·kg^{-1} for the first patient, without the use of NMBAs. All patients concurrently received remifentanil using target-controlled infusion (TCI) at a fixed effect-site concentration (Ce) of 3.0 ng·mL^{-1}. Insertion of the i-gel was attempted 90 sec after remimazolam administration, and insertion conditions were assessed. Subsequent doses of remimazolam were decreased or increased by 0.05 mg·kg^{-1}, depending on the success or failure of i-gel insertion.*

Results *The mean (standard deviation) 50% effective dose (ED_{50}) of a remimazolam bolus for successful i-gel insertion as determined by the modified Dixon's up-and-down method was 0.100 (0.027) mg·kg^{-1}. The ED_{50} and ED_{95} estimated by isotonic regression were 0.111 (83% confidence interval [CI], 0.096 to 0.131) mg·kg^{-1} and 0.182 (95% CI, 0.144 to 0.195) mg·kg^{-1}, respectively. None of the patients required treatment for hypotension or bradycardia during anesthesia induction.*

Conclusion *Based on the ED_{95} of remimazolam bolus dose determined in our study, we recommend using 0.182 mg·kg^{-1} of remimazolam in combination with remifentanil TCI at a Ce of 3.0 ng·mL^{-1} for successful i-gel insertion without NMBAs in adult patients. This regimen seems effective with a low risk of hemodynamic instability during anesthesia induction.*

Study registration *ClinicalTrials.gov (NCT05298228); first submitted 6 March 2022.*

Résumé

Objectif *Le remimazolam est une benzodiazépine à action ultra-courte récemment mise au point et utilisée pour l'induction et le maintien de l'anesthésie. Toutefois, la dose efficace en bolus de remimazolam pour l'insertion de l'i-gel® (Intersurgical Ltd., Wokingham, Berkshire,*

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Royaume-Uni) sans utiliser de bloqueurs neuromusculaires (BNM) n'a pas été bien établie.

Méthode *Cette étude a inclus 25 adultes devant bénéficier d'une intervention chirurgicale sous anesthésie générale qui étaient éligibles à l'utilisation d'un i-gel. L'anesthésie a été induite avec des doses prédéterminées en bolus de remimazolam, à partir de 0,3 mg·kg^{-1} pour la première personne, sans utiliser de BNM. Toutes les personnes anesthésiées ont reçu en parallèle du rémifentanil en perfusion à objectif de concentration à une concentration au site effecteur (Ce) de 3,0 ng·mL^{-1}. L'insertion de l'i-gel a été tentée 90 secondes après l'administration de remimazolam, et les conditions d'insertion ont été évaluées. Les doses subséquentes de remimazolam ont été diminuées ou augmentées de 0,05 mg·kg^{-1}, en fonction du succès ou de l'échec de l'insertion de l'i-gel.*

Résultats *La dose efficace moyenne (écart type) de 50 % (DE_{50}) d'un bolus de remimazolam pour une insertion réussie de l'i-gel, telle que déterminée par la méthode « up-and-down » de Dixon modifiée, était de 0,100 (0,027) mg·kg^{-1}. Les DE_{50} et DE_{95} estimées par régression isotonique étaient de 0,111 (intervalle de confiance [IC] à 83 %, 0,096 à 0,131) mg·kg^{-1} et 0,182 (IC 95 %, 0,144 à 0,195) mg·kg^{-1}, respectivement. Aucun·e patient·e n'a eu besoin de traitement pour une hypotension ou une bradycardie pendant l'induction de l'anesthésie.*

Conclusion *D'après la DE_{95} de la dose de remimazolam en bolus déterminée dans notre étude, nous recommandons d'utiliser 0,182 mg·kg^{-1} de remimazolam en association avec une perfusion à objectif de concentration de rémifentanil à une Ce de 3,0 ng·mL^{-1} pour réussir l'insertion de l'i-gel sans BNM chez la patientèle adulte. Ce schéma semble efficace avec un faible risque d'instabilité hémodynamique lors de l'induction de l'anesthésie.*

Enregistrement de l'étude *ClinicalTrials.gov (NCT05298228); première soumission le 6 mars 2022.*

Keywords bolus · i-gel® · nonparalyzed · remimazolam · remifentanil · supraglottic airway device

Since their introduction, supraglottic airway devices (SGAs) have greatly evolved and are widely used in general anesthesia and emergency situations.[1–3] Among the various SGAs, the i-gel® (Intersurgical Ltd., Wokingham, Berkshire, UK) is made of a thermoplastic elastomer with a unique noninflatable cuff and has a high success rate of insertion.[1,4,5] To ensure successful insertion of the i-gel, it is imperative to suppress coughing, gagging, and straining by maintaining an appropriate depth of anesthesia and relaxing the jaw muscles.[6,7] This is especially true in nonparalyzed patients where failure to maintain sufficient anesthesia depth can result in airway complications.[8–11]

The most commonly used hypnotic for SGA insertion without neuromuscular blocking agents (NMBAs) is propofol, which coincidentally became widely available around the time of the introduction of the laryngeal mask airway (LMA®; Teleflex, Athlone, Co. Westmeath, Ireland). While propofol alone has been proven effective for SGA insertion,[12,13] combining opioids with propofol can help suppress patient responses to stimulation and mitigate the hemodynamic effects often associated with high doses of hypnotic agents.[14]

Remimazolam is a new ultra-short-acting benzodiazepine known for its rapid onset of action, short context-sensitive half-life, and fast recovery time.[15,16] While it has been proven effective for anesthesia induction and maintenance,[17] remimazolam primarily acts as a sedative without analgesic effects and therefore benefits from the coadministration of opioids during painful procedures.[18] Given the potential for hemodynamic disturbances caused by hypnotics and opioids, it is important to establish a safe and effective dose of each component that ensures successful SGA insertion while maintaining hemodynamic stability.[14] Therefore, our study aimed to investigate the bolus dose of remimazolam that facilitates i-gel insertion without the use of NMBAs when combined with a fixed effect-site concentration (Ce) of 3.0 ng·mL^{-1} with remifentanil target-controlled infusion (TCI) in adult patients undergoing general anesthesia.

Materials and Methods

Ethics

Ethical approval for this study (protocol number 4-2021-1706) was provided by the Institutional Review Board of Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea (Chairperson, Prof. Jin Seok Kim) on 28 January 2022 and registered at ClinicalTrials.gov (NCT05298228; first submitted 6 March 2022). After providing detailed information of the study, written informed consent was obtained from the participants. This study was conducted at a single tertiary hospital (Severance Hospital, Seoul, Republic of Korea) in accordance with the principles of the Declaration of Helsinki.

Patients

Patients aged 19 yr and older, scheduled for elective surgery under general anesthesia, were screened

consecutively and were enrolled from 16 May 2022 to 4 April 2023. Patients all had an American Society of Anesthesiologists (ASA) Physical Status of I–III and were eligible for i-gel insertion. Patients meeting the following criteria were excluded from the study: refusal to participate, anticipated difficulty in face mask ventilation based on history or anatomical structure, upper respiratory tract infection, airway-related diseases such as asthma or pneumonia, risk of gastroesophageal reflux, known allergies to benzodiazepines, impaired liver or kidney function, pregnancy or breastfeeding, obesity (body mass index [BMI] > 30 kg·m^{-2}), or a history of substance abuse.

Anesthesia technique

No premedication was administered to the patients. Upon entering the operating room, noninvasive blood pressure, electrocardiography, pulse oximetry, and electroencephalography (SedLine®; Masimo Corporation, Irvine, CA, USA) monitors were applied. Remimazolam (Byfavo®; Hana Pharm Co. Ltd., Seoul, Republic of Korea) was diluted with normal saline and prepared in a 50-mL syringe at a concentration of 1 mg·mL^{-1}. Remifentanil (Ultian; Hanlim Pharm Co. Ltd., Seoul, Republic of Korea) infusion was set up as TCI using a total intravenous anesthesia pump according to the Minto model.[19]

After preoxygenation with 100% oxygen via face mask for three minutes, predetermined doses of remimazolam were administered as a bolus over 20–30 sec using the syringe pump. Simultaneously, remifentanil was continuously infused at a target Ce of 3.0 ng·mL^{-1}. Ninety seconds after the predetermined bolus dose of remimazolam was fully administered, a single experienced anesthesiologist (S. S.) blinded to the dosage of the study drug checked for loss of consciousness (LOC) by shaking the patient's shoulders and attempted to insert the i-gel without any assistance. The size of the i-gel was chosen based on the patient's weight as recommended by the manufacturer. The lubricated i-gel was gently inserted into the patient's mouth, sliding it down the hard palate until resistance was felt.[4] The success of i-gel insertion was defined by detection of a normal square-shaped capnography waveform upon manual ventilation and observation of symmetric movements of the patient's chest wall. If insertion failed because of LOC not being reached, significant patient resistance, improper positioning of the i-gel, or laryngospasm, the patient was given an additional bolus of 0.1 mg·kg^{-1} remimazolam. If another attempt at i-gel insertion failed, endotracheal intubation was performed with an intubating dose of an NMBA. General anesthesia was maintained with a standard infusion dose of remimazolam at 1–2 mg·kg^{-1}·hr^{-1} combined with a remifentanil infusion targeted to a Ce of 1.0–4.0 ng·mL^{-1}.

The bolus dose of remimazolam was predetermined by the Dixon's up-and-down method. The starting dose was set at 0.3 mg·kg^{-1} based on a previous study suggesting an optimal dose of 0.25–0.33 mg·kg^{-1} for LOC in patients under 40 yr of age.[20] If i-gel insertion was successful on the first attempt, the subsequent patient received a decreased bolus dose of remimazolam by 0.05 mg·kg^{-1}. Conversely, if insertion failed, the following patient received a bolus dose increased by 0.05 mg·kg^{-1}.

Outcomes assessment

The adequacy of i-gel insertion was determined as either a "success" or "failure." Additionally, insertion conditions were assessed using a six-category scale (Electronic Supplementary Material [ESM] eTable).[7,21] A total score for insertion conditions was calculated by adding the points assigned to categories for swallowing, coughing or gagging, head or body movements, and laryngospasm. A score of 4 points indicates optimal conditions for SGA insertion, while a score of 12 points indicates the poorest conditions for insertion.

Mean arterial pressure (MAP), heart rate (HR), and patient state index (PSI) were recorded before anesthetic induction as baseline values, and immediately before and after and ten minutes after i-gel insertion. Hypotension was defined as a MAP < 60 mm Hg and was treated with 4 mg of ephedrine when sustained for more than three minutes. Bradycardia was defined as a HR < 50 min^{-1} and was treated with ephedrine or atropine at the discretion of the attending anesthesiologist.

Postoperative hoarseness, coughing, and sore throat were assessed 30 min after the patient's arrival at the postanesthesia care unit (PACU) and on postoperative day (POD) 1. Hoarseness was graded on a four-point scale as 0 (none), 1 (mild), 2 (moderate), or 3 (severe). Cough and sore throat were also graded on a four-point scale as 0 (none), 1 (milder than the common cold), 2 (similar to the common cold), or 3 (worse than the common cold).[22]

Statistical analysis

The primary goal of this study was to determine the effective bolus dose of remimazolam associated with a 50% (50% effective dose, ED_{50}) and 95% (ED_{95}) rate of successful i-gel insertion in nonparalyzed adult patients when combined with a remifentanil TCI of 3.0 ng·mL^{-1}. We estimated the ED_{50} of a remimazolam bolus to facilitate i-gel insertion using the Dixon's up-and-down method. The Dixon's up-and-down analysis method requires at least six pairs of success/failure in the same

direction and at least 20 participants.[23–25] We therefore enrolled 25 patients in this study. To further specify the effective dose of remimazolam, we used isotonic regression using the pooled adjacent violators algorithm (PAVA) to determine ED_{50} and ED_{95} estimates along with confidence intervals (CIs) derived by bootstrapping.

Variables are presented as mean (standard deviation [SD]) for normally distributed continuous data, median [interquartile range (IQR)] for nonparametric data, and *n* (%) for categorical data. We compared baseline patient characteristics between patients in whom i-gel insertion was a "success" or "failure." We used the two-sample *t* test to compare normally distributed continuous data. For comparison of nonparametric data, we used the Wilcoxon rank sum test. We compared categorical data using the Chi square test or Fisher's exact test, as appropriate. For comparisons of hemodynamic data including MAP, HR, and PSI between the groups over time, we used a linear mixed model. To address the correlation between the time points, we incorporated an auto-correlation structure with lag one in the model. We conducted post hoc analyses with a Bonferroni correction to compare baseline with each time point (before i-gel insertion, after i-gel insertion, and ten minutes after i-gel insertion). We considered a Bonferroni adjusted $P < 0.05$ as being statistically significant. All statistical analyses were performed with R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Figure 1 shows the study flow diagram. Among 30 patients screened for eligibility, three were excluded for not meeting the inclusion criteria. After enrolment, one patient was further excluded because of an error in drug preparation and one patient because of inappropriate screening. The remaining 25 patients completed the study protocol and were included in the final analysis. Patient characteristics of the participants according to failure or success of i-gel insertion on first attempt are presented in Table 1. While no statistically significant differences in baseline characteristics were observed between the "fail" and "success" groups, it was noted that patients in the success group tended to be slightly older and shorter, and included a higher proportion of females.

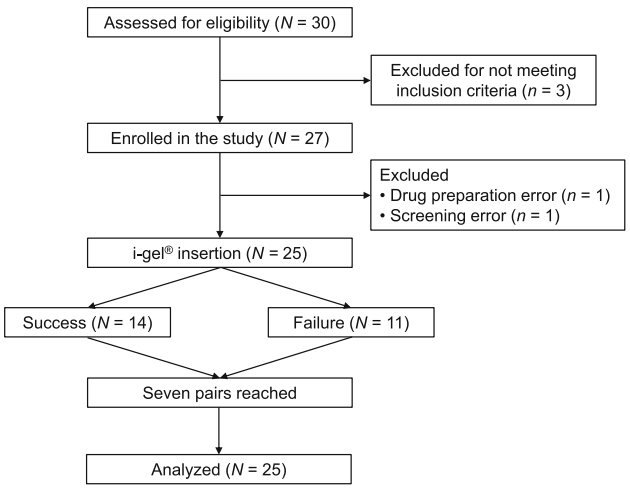

Fig. 1 Flow diagram of the study

The sequence of either the success or failure of i-gel insertion at first attempt in the 25 consecutive patients is shown in Fig. 2. Of the 11 patients in which i-gel insertion failed, four patients who received 0.05 $mg \cdot kg^{-1}$ and one patient who received 0.1 $mg \cdot kg^{-1}$ failed to reach LOC after 90 sec of remimazolam bolus dose administration. The mean (SD) ED_{50}, estimated from seven crossover pairs using the Dixon's up-and-down method, was 0.100 (0.027) $mg \cdot kg^{-1}$ (Table 2). Figure 3 illustrates the PAVA-adjusted probability of successful i-gel insertion for each dose level. The ED_{50} and ED_{95} estimates calculated by isotonic regression with PAVA were 0.111 $mg \cdot kg^{-1}$ (83% CI, 0.096 to 0.131) and 0.182 $mg \cdot kg^{-1}$ (95% CI, 0.144 to 0.195), respectively (Table 2). We performed a simulation to evaluate the coverage of the CI for ED_{95} and the results are shown in the ESM eAppendix. Among the 100 simulation trials, the estimated coverage of the 95% CI was 72%.

The trends of MAP, HR, and PSI over time at four time-points are illustrated in Fig. 4. Although both MAP and HR were found to decrease over time and at all time-points compared with baseline, none of the patients in this study required treatment for the correction of hypotension or bradycardia. Similarly, PSI also decreased over time ($P < 0.001$) and at all time- points compared with baseline ($P < 0.001$ for all time-points) but the mean (SD) values immediately before and after i-gel insertion remained relatively higher than the recommended range of PSI for general anesthesia at 62 (11) and 52 (14), respectively.

The scores for i-gel insertion conditions were lower in patients with successful i-gel insertion compared with those with failed insertion ($P < 0.001$). Among the success group, insertion conditions were suboptimal in seven patients who showed either slight swallowing movements, slight head or body movements, or both. Nevertheless, none of the patients in the success group presented with coughing, gagging, or laryngospasm (Table 3). No blood-tinged i-gel devices or oropharyngeal trauma were observed, and none of the patients required endotracheal intubation.

Table 1 Patient baseline characteristics

	Fail $N = 11$	Success $N = 14$	P value
Age (yr), median [IQR]	39 [27–51]	53 [28–57]	0.57
Sex, *n*/total *N* (%)			0.12
Male	7/11 (64%)	4/14 (29%)	
Female	4/11 (36%)	10/14 (71%)	
Height (cm), median [IQR]	166 [162–171]	163 [158–177]	0.53
Weight (kg), mean (SD)	69 (14)	71 (13)	0.68
BMI ($kg \cdot m^{-2}$), mean (SD)	24.5 (3.2)	25.7 (2.9)	0.35
ASA PS, *n*/total *N* (%)			> 0.99
I	8/11 (73%)	10/14 (71%)	
II	3/11 (27%)	4/14 (29%)	

"Fail" denotes failed i-gel® insertion at first attempt whereas "success" denotes successful i-gel insertion at first attempt

ASA PS = American Society of Anesthesiologists Physical Status; BMI = body mass index; IQR = interquartile range; SD = standard deviation

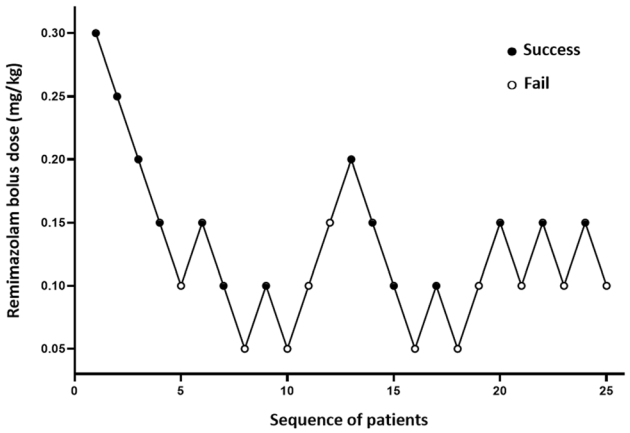

Fig. 2 Assessment of the bolus dose of remimazolam required for successful i-gel® insertion without neuromuscular blocking agents in adults using the Dixon's up-and-down method. The individual responses to i-gel insertion in 25 consecutive patients is shown with solid circles (●) indicating successful i-gel insertion and open circles (○) indicating failed insertion. The mean (standard deviation) 50% effective dose of a remimazolam bolus dose, calculated from the midpoints of pairs of "success" and "failure," was 0.100 (0.027) $mg \cdot kg^{-1}$.

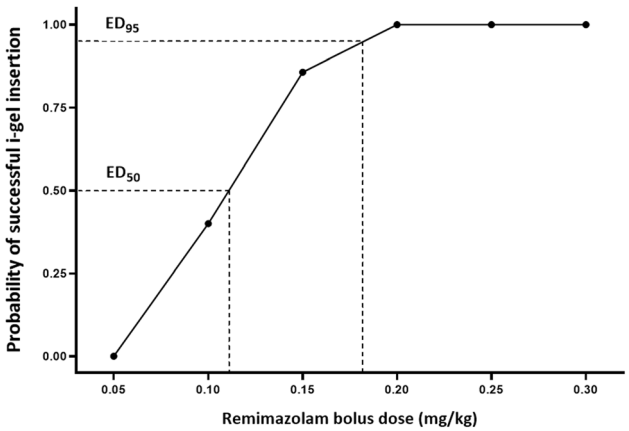

Fig. 3 Probability of successful i-gel® insertion estimated with the pooled adjacent violators algorithm. The ED_{50} of remimazolam bolus dose for i-gel insertion estimated by isotonic regression was 0.111 $mg \cdot kg^{-1}$ (83% confidence interval [CI], 0.096 to 0.131). The ED_{95} of remimazolam dose bolus was estimated to be 0.182 $mg \cdot kg^{-1}$ (95% CI, 0.144 to 0.195).

ED_{50} = 50% effective dose; ED_{95} = 95% effective dose

Table 2 Dose of remimazolam needed for i-gel® insertion in nonparalyzed adults

Dixon's up-and-down method*	
ED_{50} of remimazolam ($mg \cdot kg^{-1}$)	0.100 (0.027)
Isotonic regression method†	
ED_{50} of remimazolam ($mg \cdot kg^{-1}$)	0.111 (0.096 to 0.131)
ED_{95} of remimazolam ($mg \cdot kg^{-1}$)	0.182 (0.144 to 0.195)

*Data from the modified Dixon's up-and-down method are presented as mean (standard deviation)

†Data from the isotonic regression with the pooled adjacent violators algorithm are presented as the ED_{50} (83% confidence interval [CI]) and ED_{95} (95% CI, estimated coverage of 72%)

Discussion

In this study using Dixon's up-and-down method, we found the estimated mean (SD) ED_{50} of a remimazolam bolus for successful i-gel insertion when combined with a commonly used Ce of remifentanil in nonparalyzed adults to be 0.100 (0.027) $mg \cdot kg^{-1}$. Further, the ED_{50} and ED_{95} estimated by isotonic regression were 0.111 $mg \cdot kg^{-1}$ (83% CI, 0.096 to 0.131) and 0.182 $mg \cdot kg^{-1}$ (95% CI, 0.144 to 0.195), respectively. Coadministration of remimazolam at these specified dosages along with a remifentanil TCI at 3.0 $ng \cdot mL^{-1}$ not only facilitated i-gel

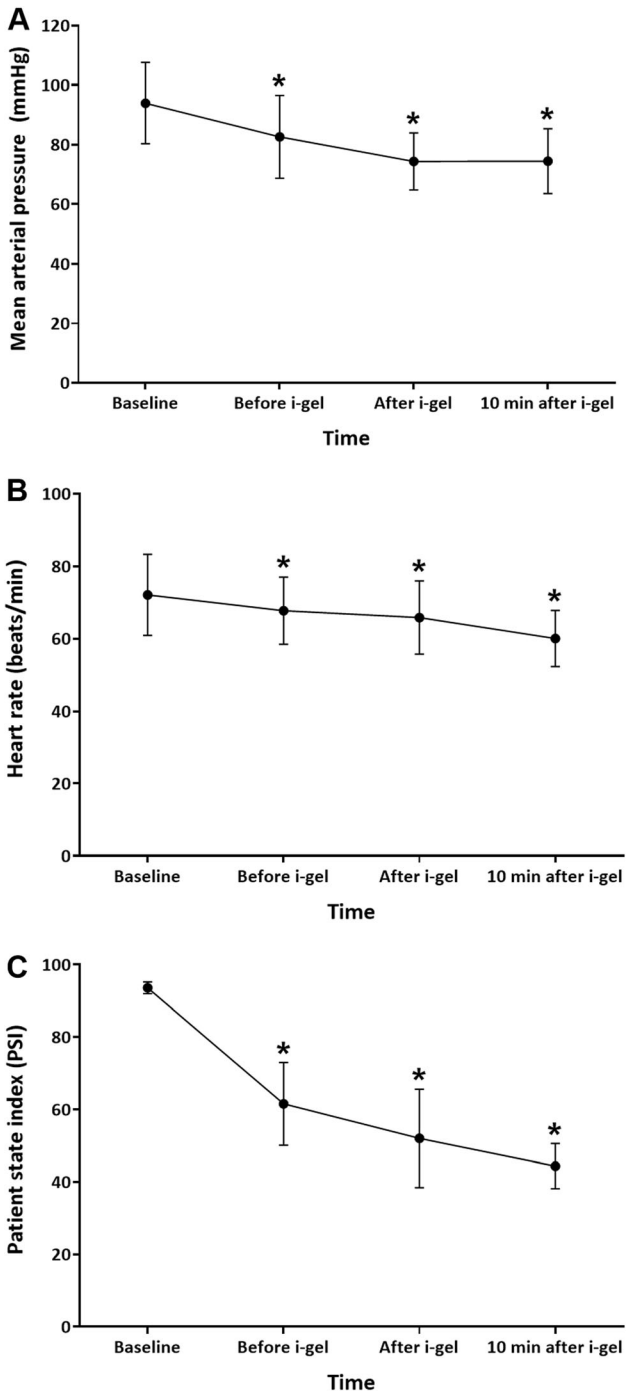

Fig. 4 Changes in (A) mean arterial pressure, (B) heart rate, and (C) patient state index during the study period. Baseline, before anesthesia induction; before i-gel®, immediately before i-gel insertion; after i-gel, immediately after i-gel insertion; ten minutes after i-gel, ten minutes after i-gel insertion. *Bonferroni adjusted $P < 0.05$ compared with the baseline value.

insertion but also ensured hemodynamic stability during anesthesia induction.

The present findings align closely with a recent study by Chae *et al.*,[20] reporting an ED_{50} of 0.11 mg·kg^{-1} and ED_{95} of 0.19 mg·kg^{-1} for achieving LOC with bolus doses of remimazolam. It is important to note that these doses are most likely insufficient for i-gel insertion when used alone. Nevertheless, when combined with a remifentanil infusion at an Ce of 3.0 ng·mL^{-1}, we observed a synergistic effect that seems to have lowered the required dose of remimazolam.[2,26] The addition of remifentanil during SGA insertion has been shown to reduce the dose requirements of propofol in previous studies. Zaballos *et al.*[14] reported a reduction of up to 60% in propofol requirements for LMA-Supreme insertion by adding remifentanil at a Ce of 5 ng·mL^{-1}. Similarly, Park *et al.*[27] found that remifentanil halved the 50% effective concentration (EC_{50}) of propofol for LMA insertion in children. Remifentanil infusion is one of the most common methods of analgesic administration during anesthesia induction and maintenance, which makes our study design closely reflective of real-world anesthesia practice.

In our initial experience with remimazolam, we found it challenging to insert an SGA using remimazolam as a standalone anesthetic, either as an infusion or bolus. We therefore opted to incorporate remifentanil along with remimazolam. The target Ce of 3.0 ng·mL^{-1} for remifentanil was based on a previous report suggesting an EC_{50} of 3.04 ng·mL^{-1} for LMA insertion.[28] By combining remifentanil TCI to mitigate response to nociceptive stimuli, we found that a relatively low dose of remimazolam was sufficient for facilitating i-gel insertion.

Currently, there are only two studies[2,29] that have investigated the dose of remimazolam for i-gel insertion without the use of NMBAs. Interestingly, both studies reported relatively higher doses of remimazolam compared with our study. In a study that was conducted under similar settings as our present study, the reported mean (SD) ED_{50} of a remimazolam bolus was 0.280 (0.048) mg·kg^{-1},[2] which is more than double that of our findings. This significant difference is noteworthy, especially considering that the target Ce for remifentanil was identical at 3.0 ng·mL^{-1}. The other study investigated the infusion rate of remimazolam for i-gel insertion with the coadministration of fentanyl.[29] The authors used 1 μg·kg^{-1} of fentanyl and attempted to insert the i-gel 2.5 min after the remimazolam infusion and found the ED_{50} and ED_{95} to be 8.8 mg·kg·hr^{-1} and 10.7 mg·kg·hr^{-1}, respectively. While it is challenging to directly compare these results to our study because of the different method of remimazolam administration, a rough conversion of total remimazolam dose from the previous study corresponds to approximately 0.37 mg·kg^{-1} and 0.45 mg·kg^{-1} for the ED_{50} and ED_{95}, respectively, which are notably higher than our findings. One important distinction between our study and the previous two studies lies in the definition of

Table 3 Insertion conditions of the i-gel® and the incidence of hoarseness, cough, and sore throat at the postanesthetic care unit and on postoperative day 1

Variable	Fail *N* = 11	Success *N* = 14	*P* value
Resistance to mouth opening	2.4 (0.5)	1.0 (0.0)	< 0.001
Resistance to insertion	2.7 (0.5)	1.0 (0.0)	< 0.001
Insertion condition score	9.9 (0.9)	4.6 (0.8)	< 0.001
Swallowing	2.9 (0.3)	1.4 (0.5)	< 0.001
Coughing and gagging	2.5 (0.5)	1.0 (0.0)	< 0.001
Head or body movement	2.8 (0.4)	1.1 (0.4)	< 0.001
Laryngospasm	1.7 (0.6)	1.0 (0.0)	0.004
Hoarseness			
PACU, 0/1/2	8/3/0 (73%/27%/0%)	10/4/0 (71%/29%/0%)	> 0.99
POD 1, 0/1/2	10/0/1 (91%/0%/9%)	12/1/1 (86%/7%/7%)	> 0.99
Cough			
PACU, 0/1/2	11/0/0 (100%/0%/0%)	14/0/0 (100%/0%/0%)	N/A
POD 1, 0/1/2	10/1/0 (91%/9%/0%)	14/0/0 (100%/0%/0%)	0.44
Sore throat			
PACU, 0/1/2	11/0/0 (100%/0%/0%)	11/3/0 (79%/21%/0%)	0.23
POD 1, 0/1/2	10/1/0 (91%/9%/0%)	7/5/2 (50%/36%/14%)	0.10

Data are shown as mean (standard deviation) or *n* (%)

Variables were scored as follows: resistance to mouth opening: nil = 1, significant = 2, undue force required = 3; resistance to insertion: nil = 1, significant = 2, undue force required = 3; swallowing: nil = 1, slight = 2, gross = 3; coughing and gagging: nil = 1, slight = 2, gross = 3; head or body movement: nil = 1, slight = 2, gross = 3; laryngospasm: nil = 1, partial = 2, total = 3; the insertion condition score was calculated by adding the points for swallowing, coughing and gagging, head or body movement, and laryngospasm (4 being the optimal condition, 12 being the poorest condition).

Hoarseness was graded as 0 (no hoarseness at all), 1 (mild hoarseness), 2 (moderate hoarseness), or 3 (severe hoarseness). Cough and sore throat were graded as 0 (no coughing or sore throat), 1 (milder than the common cold), 2 (similar to the common cold), or 3 (worse than the common cold).

N/A = not applicable; PACU = postanesthesia care unit; POD = postoperative day

successful i-gel insertion. The two previous studies defined "success" as no resistance to mouth opening (i.e., fully relaxed jaw) and no coughing or body movements. In contrast, we allowed for slightly suboptimal conditions, such as slight swallowing or body movements, as long as the patient remained fully unconscious, the i-gel was properly inserted, and lung ventilation was confirmed. We believe that, in clinical practice, it is realistic to allow for slight movements that do not hinder SGA insertion unless excessive force is required, which may result in oropharyngeal trauma for the patient. If the exact same definitions of "success" for i-gel insertion had been used, our study would have yielded higher bolus doses closer to the results of the previous studies.

Another difference between the previous studies and our study is the time interval from remimazolam administration to i-gel insertion. The previous studies allowed a time interval of 150 sec, whereas we used a shorter interval of 90 sec in our study. The decision to use the 90-sec interval was based on the time to LOC with remimazolam reported in previous studies, which is approximately 50 sec.[2,20] We also considered the time to peak effect of remifentanil, which is reported to be between 1.2 and 1.6 min according to the Minto model.[19] The i-gel has a unique gel-like consistency and structural design that resembles the larynx, resulting in minimal upper airway irritation. Previous reports have shown that the i-gel requires less propofol[30] and remifentanil[4] for successful insertion compared with the LMA. Based on this knowledge, we hypothesized that once the Ce of remifentanil is reached at the state of LOC, the i-gel can be easily inserted without having to wait for more than 90 sec after the bolus dose of remimazolam is fully administered. It should, however, be noted that we found a bolus dose of 0.05 $mg \cdot kg^{-1}$ remimazolam to be insufficient in achieving LOC within 90 sec, even when coadministered with remifentanil in all four patients that received this dosage. In addition, although our 90-sec time interval was carefully chosen based on previous evidence, it should be kept in mind that this may not always be sufficient for a full effect of remifentanil to be reached

because of the limitations of commercialized pharmacokinetic/pharmacodynamic models and the inevitable biological variability between individuals.

The main advantage of a lower dose of remimazolam and a shorter time interval of our study was the improved hemodynamic stability. Compared with our study where none of the patients required treatment for hypotension, the two previous dose-finding studies reported incidences of hypotension of 12%[2] and 46%,[29] respectively. It is always desirable to use the minimally effective dose of hypnotics to avoid unwanted side effects and for cost-effectiveness, and our study shows that a relatively lower bolus dose of remimazolam can facilitate i-gel insertion with greater hemodynamic stability when combined with remifentanil TCI of 3.0 $ng{\cdot}mL^{-1}$. These findings may be of more significance in vulnerable patients such as the elderly or those with cardiovascular comorbidities. Further studies investigating different remimazolam bolus doses at variable time intervals and Ce of remifentanil will be able to provide useful information for the application of remimazolam in general anesthesia.

Our study has several limitations. First, the study population consisted mainly of young and healthy adults with BMIs of 30 $kg{\cdot}m^{-2}$ or lower. It is important to recognize that dosage requirements for remimazolam are likely to differ for the elderly[20,31] and individuals who are obese.[32] Given that these patient subpopulations constitute a significant proportion of the global population, future studies are warranted to offer practical insights into the application of remimazolam protocols in a wider range of BMI groups. Second, we used TCI for remifentanil administration with a fixed Ce of 3.0 $ng{\cdot}mL^{-1}$ throughout the study. This may limit the generalizability of our protocol in clinical settings where TCI is not the preferred method or is unavailable, and our findings do not offer an alternative dosage option for a different Ce. Further research is needed to investigate how various modes of remifentanil administration may impact the required dosage of remimazolam for SGA insertion. Third, our study focused specifically on the i-gel insertion and therefore our results may not be applicable to other commonly used SGAs. Each SGA has its own unique properties, and drug requirements have been reported to be different between different SGAs.[4,30,33] Fourth, although all patients were checked for LOC before attempting to insert the i-gel, we did not record the exact time to LOC. Furthermore, the method we employed to assess LOC in our study (shaking the patient's shoulders) is subject to issues of objectivity and reproducibility. Incorporating data relevant to LOC that is obtained through objective monitoring methods in future studies would provide further insights into the effects of remifentanil coadministration with remimazolam. Finally, our study was designed with the Dixon's up-and-down method aimed at targeting ED_{50}, but we estimated extreme percentile ED_{95}. Given that data are primarily collected around ED_{50} in the up-and-down method, estimates of ED_{95} may be unreliable, as seen with the estimated coverage of 72%.[34,35] Further research is warranted to estimate higher target percentiles using alternative designs such as a biased coin design,[25] developed for targets other than median.

In conclusion, the ED_{50} of the bolus dose of remimazolam required for i-gel insertion with the coadministration of remifentanil TCI at a Ce of 3.0 $ng{\cdot}mL^{-1}$ in nonparalyzed healthy adults was 0.100 (0.027) $mg{\cdot}kg^{-1}$. Considering the estimated ED_{95}, which was 0.182 $mg{\cdot}kg^{-1}$ (95% CI, 0.144 to 0.195), we suggest using a remimazolam bolus dosage of 0.182 $mg{\cdot}kg^{-1}$ in combination with remifentanil when inserting the i-gel without NMBAs. This regimen seems effective and safe in terms of hemodynamic stability in patients undergoing general anesthesia using the i-gel.

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