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The influence of sex on the dosage of remimazolam co-administered with remifentanil for loss of consciousness in adult patients: an up-and-down sequential allocation trial

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Abstract

Background This study aimed to determine the 50% effective dose of remimazolam co-administered with remifentanil for loss of consciousness in men and women as well as to investigate whether there are between-sex differences.

Methods Using a modified Dixon's up-and-down allocation approach, we sequentially enrolled male and female patients aged 19–60 years with American Society of Anesthesiologists class I or II who were scheduled for robotic surgery. For both sexes, the starting remimazolam dose was 0.15 mg/kg, with a step size of 0.05 mg/kg. After achievement of a target effect-site concentration 2.0 ng/ml of remifentanil, and administration of a bolus dose of remimazolam, we assessed whether adequate loss of consciousness (defined as a Modified Observer's Assessment of Alertness/Sedation scale score < 2 within 2 min) was achieved.

Results We included 22 male and 22 female patients. Based on Dixon's up-and-down method, the 50% effective dose of remimazolam (mean ± standard error) was 0.13 ± 0.01 mg/kg and 0.17 ± 0.01 mg/kg in the male and female groups, respectively ($P = 0.34$). Isotonic regression analysis revealed that the 95% effective dose (95% confidence interval) was 0.19 (0.18–0.20) mg/kg in the male group and 0.29 (0.29–0.30) mg/kg in the female group.

Conclusions There was no between-sex difference in the 50% effective dose of remimazolam for loss of consciousness; however, the 95% effective dose was significantly higher in female patients than in male patients.

Trial registration This study protocol was registered at Clinical Research Information Service (CRIS No. KCT0007951, 02/12/2022).

Keywords Remimazolam, Sex, Deep sedation, General anesthesia

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Background

Remimazolam is a short-acting benzodiazepine derivative commonly used for procedural and deep sedation in patients undergoing surgical procedures [1]. Similar to propofol, it allows rapid anesthesia induction and recovery from anesthesia; moreover, it has a favorable safety profile in terms of hemodynamic stability [2]. Furthermore, given the availability of flumazenil as a specific antagonist, remimazolam is suitable for not only general anesthesia but also short diagnostic or therapeutic procedures. Continuous remimazolam infusion is the preferred administration method given its short context-sensitive half-life; however, there is a need to establish a single-dose protocol for this drug in clinical settings. It is noteworthy that many intravenous sedatives are commonly administered by single bolus injections. Accordingly, there have been numerous studies on the single-dose remimazolam administration [3–5].

It is important to consider age and sex when determining the effective remimazolam dosage for anesthesia induction. We previously examined the influence of age on the remimazolam bolus dose required to achieve loss of consciousness (LOC) without the use of concomitant drugs and found no significant differences between different ages [3]. However, the appropriate dosage for LOC according to sex remains unclear. Sex differences have been reported in the sedative effects of midazolam, which is another benzodiazepine [6]. We hypothesized that there are between-sex differences in the remimazolam dose required to achieve LOC. Accordingly, we aimed to determine the 50% effective dose (ED_{50}) and 95% effective dose (ED_{95}) of remimazolam in men and women when co-administered with remifentanil for LOC during anesthesia induction.

Methods

Patient enrolment

This prospective study was conducted at a tertiary medical center between January 2023 and February 2023. The study protocol was approved by the Institutional Review Board of the Ajou University Hospital (AJOUIRB-IV-2022-443) and registered with the Clinical Research Information Service (CRIS No. KCT0007951, 02/12/2022). All patients provided written informed consent before participating in the study and methods were conducted in accordance with the Declaration of Helsinki.

We enrolled adult patients aged 19–60 years with an American Society of Anesthesiologists physical status of 1 or 2 who were scheduled for robotic surgery. The exclusion criteria were as follows: obesity (body mass index > 30 kg/m^2), history of allergy to benzodiazepines or opioids, history of habitual use of benzodiazepines or opioids, communication difficulties such as hearing disability or mental disorder, significant renal or hepatic dysfunction (estimated glomerular filtration rate < 30 mL/min/1.73 m^2, Child Pugh scale ≥ 7), and pregnancy or lactation. Enrolled patients were allocated to two groups according to sex.

Intervention

All patients were admitted to the operating room without receiving any premedication. Standard monitoring, including electrocardiography, non-invasive blood pressure measurement, and pulse oximetry, was initiated. The anesthetic depth was assessed by attaching a UniCon (ADMS™, Anesthetic Depth Monitor for Sedation, Unimedics CO., LTD., Seoul, Korea) sensor to the patient's forehead. For anesthesia induction, effect-site target-controlled infusion of remifentanil was initiated using an infusion device (Orchestra® Base Primea; Fresenius Vial, Brezins, France), with a target effect-site concentration (Ce) of 2.0 ng/ml. Once the Ce of remifentanil reached 2.0 ng/ml, remimazolam bolus was administered. Remimazolam was prepared at a concentration of 1 mg/ml in a 50 ml syringe and was loaded on an infusion pump (Agilia SP TIVA, Fresenius Kabi AG, Bad Homburg, Germany). Subsequently, an anesthesiologist entered the pre-calculated bolus dose of remimazolam and set the loading duration to 1 min. Another anesthesiologist who was blinded to the bolus dose of remimazolam evaluated the patient's LOC for 2 min immediately after completion of remimazolam administration using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale [7]. The MOAA/S scale was chosen to promptly assess the patient's anesthetic depth, since some delay is inevitable with anesthetic depth monitors [8]. LOC was defined as a MOAA/S scale score ≤ 1; moreover, 'successful LOC' was defined as LOC occurring within 2 min of the completion of remimazolam infusion. During this period, no additional anesthetic agents were administered. Based on a previous study that reported a mean (SD) LOC time of 102.0 (26.6) s at an infusion rate of 6 mg/kg/h [2], we assumed that assessing LOC within 2 min reflects clinical reality. For patients not exhibiting LOC, a remimazolam infusion at 6 mg/kg/h was promptly initiated, as recommended by the manufacturer. Once LOC was achieved, the remimazolam infusion rate was reduced to 1–2 mg/kg/h.

If the patient's systolic arterial blood pressure (SBP) decreased by > 30% of the baseline or the mean arterial blood pressure (MAP) dropped below 65 mmHg during induction, 4–8 mg ephedrine was administered. In case the patient's heart rate was < 50 beats per minute, atropine (0.5 mg) was administered. After 1 min of remimazolam loading and 2 min of consciousness assessment, continuous remimazolam infusion (1–2 mg/kg/h) was started with the Ce of remifentanil set at 3.0 ng/ml.

Furthermore, a neuromuscular blocking agent (0.6 mg/kg rocuronium) was administered for endotracheal intubation. Vital signs, including blood pressure, heart rate, and pulse oximetric saturation (SpO_2), as well as the UniCon index, were collected at the following five time points: prior to administration of anesthetic drugs (T0), immediately after completion of remimazolam loading (T1), upon achievement of LOC (T2), and 1 min (T3) and 2 min (T4) after the end of remimazolam loading. Additionally, we recorded the use of medications to control the blood pressure and heart rate during the induction period.

Patients were sequentially enrolled using a modified Dixon's up-and-down allocation approach [9]. Specifically, the patients were continuously enrolled until both groups reached at least six crossover pairs in the same direction and until there were a total of ≥20 patients [10]. Based on previous studies [2, 3, 5], the starting dose of remimazolam was set at 0.15 mg/kg while the change in the adjacent remimazolam dose was set at 0.05 mg/kg in both groups. The modified Dixon's up-and-down method involves administration of a drug to a group of patients, where the dose used for each subsequent patient is adjusted according to the previous patient's response. Therefore, in case of successful LOC, the dose for the next patient was decreased by 0.05 mg/kg; otherwise, the dose was increased by 0.05 mg/kg. After extubation, the patients were monitored for postoperative nausea and vomiting, sore throat, and recall for 60 min in the post-anesthetic care unit.

Outcome variables

The primary outcome was the ED_{50} of remimazolam required to achieve adequate LOC. The secondary outcomes included the ED_{95} of remimazolam for achieving adequate LOC, time from the end of remimazolam infusion to LOC, blood pressure, heart rate, and UniCon index throughout the study period.

Statistical analyses

The ED_{50} of remimazolam was calculated as the mean value of the midpoint for each crossover pair using Dixon's up-and-down method. To determine the remimazolam dose, ED_{50} and ED_{95} values were determined using isotonic regression with a pooled adjacent violator algorithm (PAVA) in order to adhere to the prediction in a monotonically increasing dose-effect relationship along with confidence intervals (CIs) [11]. In case the ED_{50} and ED_{95} values did not overlap at the levels of 83% CI and 95% CI estimated by a bootstrapping approach, the null hypotheses of equal EDs were rejected at an α of 0.05 [12].

Categorical variables were analyzed using the chi-square or Fisher's exact test and were presented as numbers (frequencies). Continuous variables were analyzed using Student's t-tests or Mann-Whitney U test and were presented as means ± SD or medians (25th to 75th quartile), as appropriate. Measured variables were analyzed using one-way repeated measures analysis of variance. We performed within-group comparisons of the vital signs and UniCon index at different time points. When the model revealed a significant interaction between group and time, post hoc analysis was performed to identify the time points that significantly differed. Statistical significance was set at $P<0.05$. All statistical analyses were performed using the SPSS (version 25.0; IBM Corporation, Armonk, NY, USA) and R software (version 4.0.5).

Results

This study enrolled 44 patients (22 male and 22 female patients; Fig. 1). Table 1 shows the demographic characteristics of the patients. Figure 2 shows the remimazolam dose associated with the success or failure of LOC in each consecutive patient. Using modified Dixon's up-and-down method, the mean ± SE (standard error) of ED_{50} was 0.13 ± 0.01 mg/kg in the male group and 0.17 ± 0.01 mg/kg in the female group ($P=0.34$). Based on the isotonic regression analysis, the ED_{50} (83% CI) was 0.14 (0.12–0.16) mg/kg in the male group and 0.14 (0.10–0.21) mg/kg in the female group. Additionally, the ED_{95} (95% CI) was 0.19 (0.18–0.20) mg/kg in the male group and 0.29 (0.29–0.30) mg/kg in the female group, respectively (Table 2). Since the ED_{95} values did not overlap at the 95% CI level, the remimazolam dose required for deep sedation within 2 min was significantly higher in the female group than in the male group. Figure 3 depicts the isotonic regression analysis performed using PAVA and bootstrapping approaches.

The time from end of remimazolam infusion to LOC was 95.6 ± 12.1 s and 95.1 ± 16.3 s in the male and female groups, respectively ($P=0.93$). During the induction period, the blood pressure, heart rate, SpO_2, and UniCon index showed similar trends over time in both groups (Fig. 4). In both groups, the blood pressure significantly decreased throughout the study period; however, none of the patients experienced hypotension (SBP decreased by >30% of the baseline or MAP < 65 mmHg) (Fig. 4A). Further, heart rate showed a non-significant increase in both groups at T1 (Fig. 4B). One patient experienced nausea in the recovery room.

Discussion

This study investigated the dose of remimazolam bolus required to induce general anesthesia in men and women when co-administered with remifentanil. There was no between-sex difference in the ED_{50} of remimazolam for

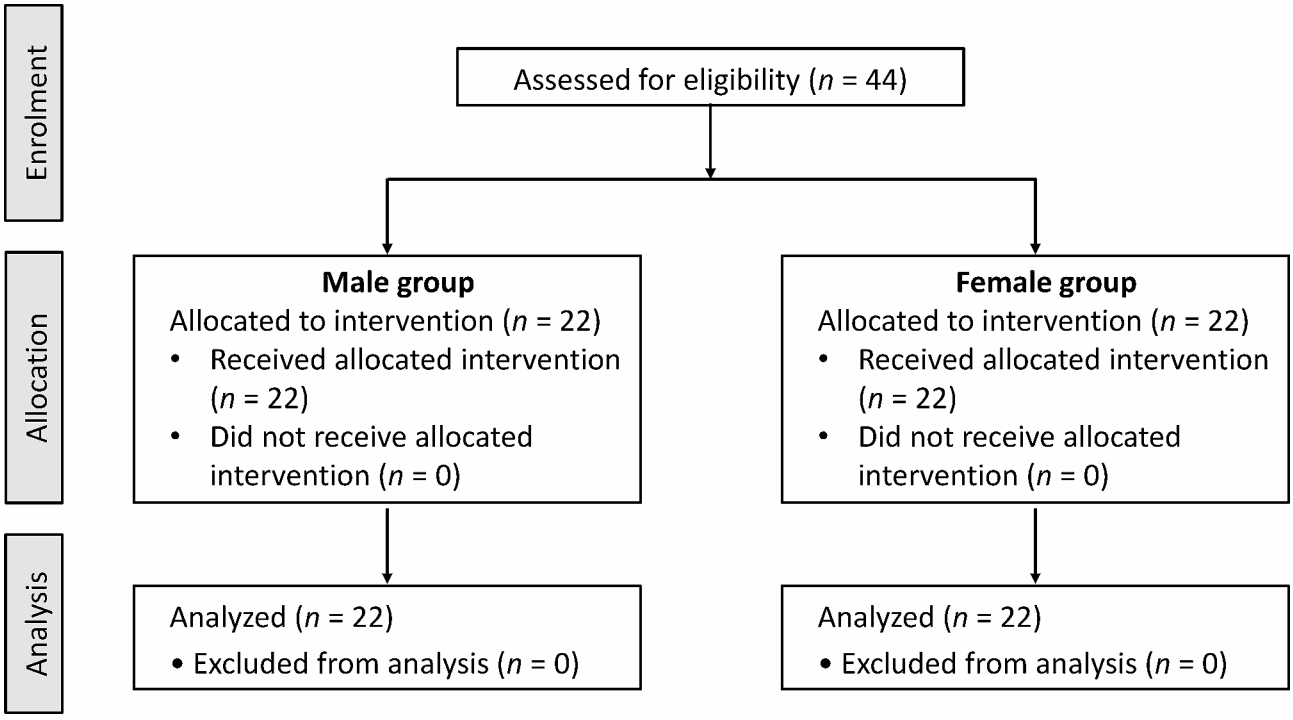

Fig. 1 Consort flow diagram of included patients

Table 1 Patient demographics and clinical characteristics

Variable	Male (N = 22)	Female (N = 22)	P-value
Age (yr)	46.5 ± 9.4	41.8 ± 9.9	0.110
Weight (kg)	75.3 ± 8.9	60.3 ± 7.2	< 0.001
Height (cm)	174.3 ± 6.3	161.9 ± 4.6	< 0.001
BMI (kg/m^2)	24.8 ± 2.2	23.0 ± 3.0	0.035
ASA classification, n (%)			0.486
I	15 (68.2)	18 (81.8)	
II	7 (31.8)	4 (18.2)	
Time to LOC (sec)	95.6 ± 12.1	95.1 ± 16.3	0.930
Preoperative laboratory data			
Aspartate aminotransferase (IU/L)	20.6 ± 6.7	20.6 ± 14.5	> 0.999
Alanine aminotransferase (IU/L)	23.5 ± 1.0	18.6 ± 16.8	0.247
Serum creatinine (mg/dL)	0.9 ± 0.1	0.7 ± 0.1	< 0.001
Albumin (g/dL)	4.8 ± 0.3	4.6 ± 0.3	0.030
Type of robotic surgery, n (%)			
Head and neck surgery	3 (13.6)	1 (4.5)	
Thymectomy	0 (0.0)	1 (4.5)	
Cholecystectomy	14 (63.6)	6 (27.3)	
Gastrectomy	2 (9.1)	0 (0.0)	
Colorectal surgery	1 (4.5)	0 (0.0)	
Nephrectomy	1 (4.5)	1 (4.5)	
Adrenalectomy	1 (4.5)	0 (0.0)	
Gynecologic surgery	0 (0.0)	13 (59.1)	

Values are presented as mean ± standard deviation or number (%)

The number of patients for 'Time to LOC (sec)' is 11 in both the male and female groups

BMI: body mass index, ASA: American Society of Anesthesiologists, LOC: loss of consciousness

LOC; however, the ED_{95} value was significantly higher in female patients than in male patients.

The present investigation contributes to understanding the sex-specific dosing requirements for remimazolam, an anesthetic with growing clinical use. Understanding these specific dosage requirements for different demographics can enhance patient safety by reducing the risk of both underdosing and overdosing. The findings lay the groundwork for further research into the pharmacodynamics and pharmacokinetics of remimazolam.

Various factors may contribute to the sex differences in the required remimazolam dose. First, female sex hormones may contribute to pharmacokinetic and pharmacodynamic differences with remimazolam. Specifically, female sex hormones such as estrogen and progesterone may influence hippocampal gamma-aminobutyric acid receptors, which are targets of benzodiazepines [13–15]. A previous study showed that with the same midazolam dose per body weight, the sedation was deeper in men than in women [6]. Second, there are sex-related metabolic differences. Variations in enzyme activity and expression may influence the breakdown and clearance of remimazolam [16]. Carboxylesterase (CES) 1 is recognized as the specific enzyme responsible for metabolizing remimazolam [17, 18]; additionally, it accounts for 80–95% of the total hydrolytic activity in the liver [19]. Hepatic CES1 protein expression is higher in women compared than in men, which suggests that women experience relatively faster conversion of remimazolam to its

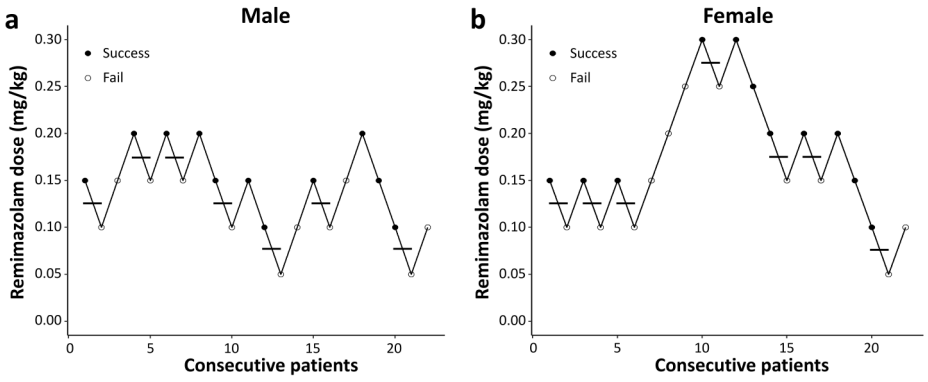

Fig. 2 Responses of consecutive patients using Dixon's up-and-down method in the (**a**) male and (**b**) female groups. A solid circle denotes successful loss of consciousness; an open circle denotes failure of loss of consciousness; horizontal bar represents crossover midpoints (success-to-failure)

Table 2 ED_{50} and ED_{95} of remimazolam for males and females

	Male (n = 22)	Female (n = 22)	P value
Dixon's up-and-down method			
ED_{50}, mg/kg	0.13 ± 0.01	0.17 ± 0.04	0.34
Isotonic regression method			
ED_{50}, mg/kg	0.14 (0.12, 0.16)	0.14 (0.10, 0.21)	
ED_{95}, mg/kg	0.19 (0.18, 0.20)	0.29 (0.29, 0.30)	

Data from Dixon's up-and-down method are presented as the mean ± standard error. Data from the isotonic regression method were the ED_{50} (83% CI) and ED_{95} (95% CI). ED_{50}, effective dose in 50% of the sample; ED_{95}, effective dose in 95% of the sample; CI, confidence interval, LOC: loss of consciousness

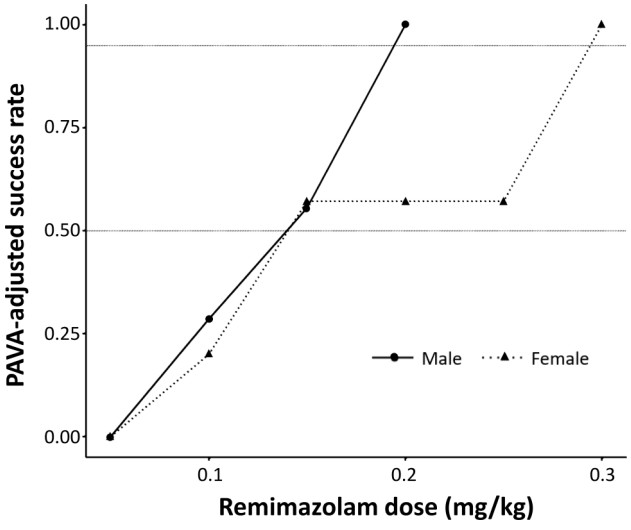

Fig. 3 The pooled adjacent violators algorithm (PAVA)-adjusted success rate. Black dots and triangles represent the success rate of each dose of remimazolam

inactive form [20]. However, in our study, there was no between-sex difference in the ED_{50} of remimazolam for LOC; however, the ED_{95} value was significantly higher in female patients than in male patients. There are several possible explanations for these findings. First, the remimazolam onset time may be longer than 2 min in some patients. We evaluated LOC 2 min after remimazolam administration, since we considered 2 min to be clinically meaningful. However, a previous study reported that >150 s were required to definitely ensure LOC [21]. Therefore, setting a cutoff value of >150 s may have yielded different results. Second, the concomitant use of opioids may have yielded different results. Given the synergistic effect of the concomitant administration of remimazolam and remifentanil [22], the results may not be interpreted solely based on the existing pharmacokinetic/pharmacodynamic model of remimazolam. Moreover, the onset time of remimazolam may vary depending on the timing of opioid administration [21]. Although there are sex differences in the effects of remifentanil [23, 24], the Minto model used for remifentanil includes sex as a variable. However, there still may be sex differences in the effects of remifentanil, which may have influenced the required remimazolam dose. Another consideration is that the study population size was not designed to accurately determine ED_{95}. Figure 2 illustrates that the success rate for males progressively increases as the concentration rises: 0% at 0.05 mg/kg, 29% at 0.1 mg/kg, 56% at 0.15 mg/kg, and 100% at 0.2 mg/kg. For females, however, the success rate increases up to 0.2 mg/kg but decreases to 33% at 0.25 mg/kg, and then increases again to 100% at 0.3 mg/kg. If a larger number of subjects were included, the probability of LOC might have increased with the drug dose. However, due to the relatively small number of patients included in the study, calculated based on the requirements of Dixon's up-and-down method, the number of patients may not have been sufficient to accurately determine ED_{95} using isotonic regression with the PAVA.

Several studies have investigated the pharmacokinetics and pharmacodynamics of remimazolam as well as their sex differences, but the results remain controversial, similar to our study. Wiltshire et al. [25] reported no significant influence of sex on pharmacokinetics. However, in

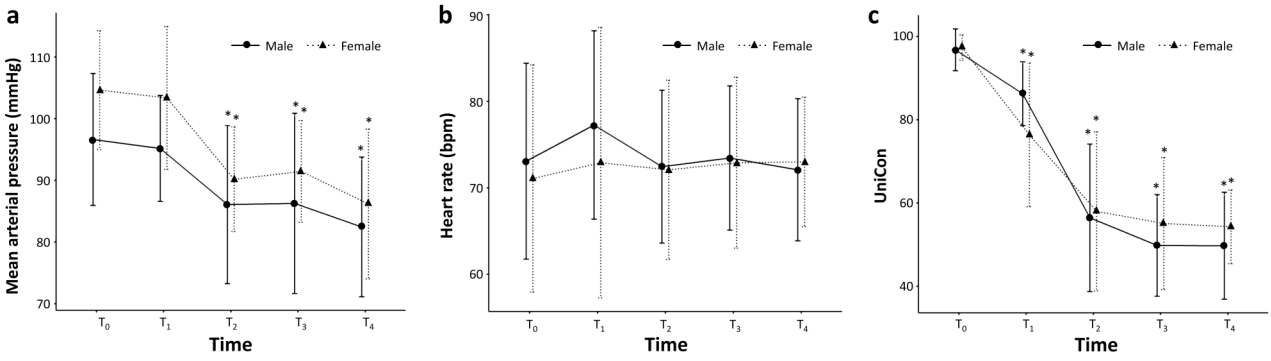

Fig. 4 Changes in (**a**) mean arterial pressure, (**b**) heart rate, and (**c**) depth of anesthesia measured by UniCon during study period. Data are represented as the mean ± standard deviation. T_0, baseline; T_1, immediately after remimazolam injection; T_2, loss of consciousness; T_3, 1 min after end of remimazolam injection; T_4, 2 min after end of remimazolam injection. *$P < 0.05$ compared to baseline

the pharmacodynamics model using the Bispectral Index (BIS), sex was a significant predictor of IC_{50}, which refers to the drug concentration that causes BIS to decrease to 50% from the baseline BIS. Specifically, they found that men were two-fold more sensitive than women [25]. Zhou et al. [26] observed no sex differences in the volume of the central compartment; however, there was an 11% between-sex difference in clearance. Since the terminal half-life of remimazolam after bolus administration is 34–60 min [27], the distribution phase, rather than metabolism or clearance, significantly influenced our findings regarding the primary outcome. During the distribution phase, the important pharmacological variables are the volume of distribution (Vd) and Ke0 (blood-brain equilibration rate constant), which determines the concentration at the effect site [28]. Since previous studies have reported sex differences in the IC_{50} but not Vd, sex might affect Ke0. Moreover, Lohmer et al. [21] reported that compared with men, women required a higher infusion rate to achieve adequate sedation and shorter time to extubation.

This study has several limitations. First, we did not consider the hormonal status of female patients. The levels of female sex hormones, including progesterone and estrogen, vary depending on the menstrual cycle or menopause, which may influence the metabolism and efficacy of remimazolam. Second, the ED_{50} of remimazolam is limited in its guidance of clinical dosing, and the ED_{95} or ED_{99} value may be more practical in actual clinical settings [29]. The ED_{95} calculated using Dixon's up-and-down approach with a focus on ED_{50} may not yield a reliable value. To obtain ED_{95}, it is more appropriate to use a biased coin approach or a continual reassessment method [30]. Therefore, further studies to evaluate the ED_{95} or ED_{99} of remimaozlam for inducing LOC may provide more accurate dosage requirements for different sexes. Third, the use of ADMS™ to monitor the hypnotic effect may limit the comparability of our findings with other publications that have used different, more widely used monitors to evaluate hypnosis. However, monitoring devices using mono-spectral power analysis and an Adaptive Neural Fuzzy Inference System (ANFIS), including UniCon (ADMS™), are relatively well-validated indices and have been reported to maintain acceptable correlation with the BIS [31, 32]. Forth, sample size was estimated using the Dixon' up-and-down allocation approach. Although this sequential method is efficient and convenient, the small sample size may be insufficient to confirm differences in secondary outcomes between the two groups.

Conclusions

In conclusion, there was no between-sex difference in the ED_{50} of remimazolam for LOC; however, the ED_{95} value was significantly higher in female patients than in male patients. Therefore, there is insufficient evidence to suggest that remimazolam in combination with remifentanil should be administered differently according to sex. Further studies on the ED_{95} of remimazolam are required to establish an appropriate dose for each sex.

Abbreviations

BIS	Bispectral index
Ce	Effect-site concentration
CES	Carboxylesterase
CI	Confidence interval
ED	Effective dose
LOC	Loss of consciousness
MAP	Mean arterial blood pressure
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
PAVA	Pooled adjacent violator algorithm
SBP	Systolic arterial blood pressure (SBP)
SE	Standard error
Vd	Volume of distribution

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Author contributions

JO: conduction of study, acquisition of data, analysis and interpretation of data, and manuscript preparation and revision. DHK: conduct of study and

acquisition of data. GC: conduct of study and acquisition of data. JHK: study conception and design. HBJ: study conception and design, and interpretation of data. SYP: conception and design of study and manuscript revision. JB: conception and design of study, conduction of study, planning, analysis and interpretation of data, and manuscript preparation and revision.

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Data availability
The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Ajou University Hospital Institutional Review Board (AJOUIRB-IV). The trial was registered prior to the first patient enrollment at cris.nih.go.kr (ref no.: KCT).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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