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Determination of the 95% effective dose of remimazolam to achieve loss of consciousness during anesthesia induction in different age groups

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Background: Remimazolam is a new ultra short-acting benzodiazepine originally developed as an improved version of midazolam. Recent studies have demonstrated non-inferiority of remimazolam to propofol in general anesthesia. However, to date, few studies have investigated the induction bolus dose of remimazolam required to achieve general anesthesia. We aimed to determine the 95% effective dose (ED₉₅) of remimazolam bolus required to achieve loss of consciousness (LOC) and the appropriate doses for different age groups.

Methods: Patients aged 20–79 years with the American Society of Anesthesiologists physical status of I or II were enrolled in this study. A total of 120 patients were included representing young, middle-aged, and elderly groups. Loss of eyelash reflex and verbal response after the administration of remimazolam was considered successful LOC. The ED₉₅ of remimazolam was determined using a biased coin up-and-down design with sequential allocation and the isotonic regression method.

Results: The ED₉₅ of remimazolam for induction of general anesthesia was 0.367 mg/kg (95% CI [0.277, 0.392]) in the young group, 0.369 mg/kg (95% CI [0.266, 0.394]) in the middle-aged group, and 0.249 mg/kg (95% CI [0.199, 0.288]) in the elderly group. During the study period, none of the patients required rescue medications for hypotension or bradycardia.

Conclusions: This study investigated the ED₉₅ of remimazolam bolus for anesthesia induction. The precise dosing of the ED₉₅ can help maintain hemodynamic stability during the induction of anesthesia.

Keywords: General anesthesia; Hypnotics and sedatives; Intravenous anesthesia; Remimazolam; Unconsciousness; Vital signs.

Introduction

Intravenous anesthetics are some of the most commonly used sedative induction agents because of their ease of delivery and swift onset as they rapidly diffuse from the blood to the brain without concerns regarding airborne contamination that may be associated with inhalation anesthetics [1,2]. Propofol is currently the most popular intravenous anesthetic, but it has been reported to produce adverse effects such as hemodynamic instability, respiratory depression, and injection pain [3–6]. Compared to propofol, midazolam causes less hemodynamic depression and produces anterograde amnesia; however, its slow, variable induction time and accumulation of active metabolites make it

inferior for general anesthesia [7–9].

Remimazolam was designed considering these shortcomings of midazolam. It is an ultra-short-acting benzodiazepine that produces equivalent sedative effects but is rapidly hydrolyzed in the body to an inactive metabolite. Consequently, remimazolam exhibits a shorter and more predictable duration of action than the current benzodiazepines [10–13]. In recent studies, the non-inferiority of remimazolam to propofol has been demonstrated in general anesthesia [14,15]. Several studies have reported the remimazolam dose for loss of consciousness (LOC) that was calculated from the continuous infusion of remimazolam (6 and 12 mg/kg/h) [15,16]. However, in clinical practice, anesthesia is commonly induced by a single bolus injection of intravenous sedatives. To date, few studies have explored the required induction bolus dose of remimazolam for general anesthesia [17]. This study aimed to investigate the 95% effective dose (ED₉₅) of remimazolam bolus for LOC and determine the appropriate doses for different age groups.

Materials and Methods

This study was approved by the Institutional Review Board of Ajou University Hospital (IRB no. AJIRB-MED-INT-21-521) and was registered at Clinical Research Information Service (CRIS no. KCT0006866). The study was conducted at a tertiary medical center, between December 2021 and March 2022. All patients were provided with adequate information regarding the study, and written informed consent was obtained from all patients. This study was conducted in accordance with the Helsinki Declaration-2013.

Patients

Patients aged 20–79 years with an American Society of Anesthesiologists physical status (ASA-PS) I or II, who were scheduled to receive general anesthesia were enrolled in this study. Patients were stratified into different age groups: young (20–39 years), middle-aged (40–59 years), and elderly (60–79 years) groups, with 40 patients enrolled in each group. The exclusion criteria were as follows: 1) body mass index > 30 kg/m² or < 20 kg/m², 2) allergy to benzodiazepines, 3) use of opioids, alcohol, benzodiazepines, and over-the-counter sleep aids, 4) communication difficulties (e.g., history of hearing disability, mental disorder, or cognitive impairment), and 5) pregnancy.

Anesthesia

No premedication was administered prior to induction, and as

the patients were transferred to the operating room, standard monitors were applied. To monitor vital signs, non-invasive blood pressure, electrocardiography, and pulse oximetry were performed. In addition, a bispectral index (BIS) monitor (A-2000™, Aspect Medical Systems, USA) was used to assess the depth of anesthesia. Before induction of anesthesia, each patient performed spontaneous breathing with 100% oxygen for pre-oxygenation. Remimazolam was prepared at 1 mg/ml, and its predetermined dose was administered as a bolus intravenous injection using a syringe pump by an anesthesiologist who calculated its induction dose. The other anesthesiologist, who was blinded to the dose of remimazolam, checked for LOC in the patient over 3 min. No additional agents were administered during this period. If the patient's mean arterial blood pressure (MAP) was < 65 mmHg during induction, 4 mg of ephedrine was administered. If a heart rate (HR) of < 50 beats per min was observed, atropine (0.5 mg) was used. Loss of eyelash reflex and verbal response after bolus administration of remimazolam was considered successful LOC. After the end of the 3-min study period, we used an inhalation agent, an opioid analgesic, and a neuromuscular blocking agent to obtain deeper analgesia and muscle relaxation for endotracheal intubation. The baseline MAP, HR, oxygen saturation, and BIS of all patients were recorded prior to remimazolam administration (T0), and these parameters were also recorded at 1 min (T1) and 3 min after administration (T2).

We used a biased coin up-and-down method to determine the ED₉₅ of remimazolam [18,19]. According to a previous study, patients who received continuous intravenous remimazolam at 6 and 12 mg/kg/h, successfully achieved LOC, and the accumulated mean dose ± SD was 0.17 ± 0.04 mg/kg and 0.29 ± 0.08 mg/kg, respectively [15]. With reference to this study, an initial dose of 0.2 mg/kg was used for all groups. The next dose of remimazolam was determined according to the success or failure of induction in the previous patient. The increase or decrease in the next dose was set at 0.05 mg/kg. If the first patient failed to achieve LOC, the dose of remimazolam for the next patient was increased by 0.05 mg/kg. If the induction was successful, the next patient's dose was determined by a randomly selected card. In total, 19 cards were prepared, and the same dose was administered with a probability of 18/19 (≈ 0.95), and with a probability of 1/19 (≈ 0.05), the dose for the next patient was decreased by 0.05 mg/kg.

Statistical analysis

In the biased coin up-and-down method, the behavior of the estimated parameters can be stabilized with 40 participants using

the Monte Carlo simulation [20]. Therefore, we enrolled 40 patients in each group.

Data are presented as mean ± SD or number of patients. Continuous variables were analyzed using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test, depending on the normality test results. The normality of all continuous variables, except for the ED₉₅, was assessed using the Shapiro–Wilk test. Categorical variables were analyzed using the chi-square test. Hemodynamic and BIS variables were analyzed using one-way repeated-measures ANOVA. Subsequently, post-hoc analysis using a paired sample t-test was performed to determine whether there was a within-group difference in the hemodynamic and BIS variables from the baseline.

The ED₉₅ was determined using isotonic regression with a pooled adjacent violators algorithm (PAVA) to adhere to prediction in a monotonically increasing dose–effect relationship, and a bootstrapping approach was used to produce 95% CIs for estimation [19].

Statistical analyses were performed using R Statistical Software (version 4.05; R Foundation for Statistical Computing, Austria) and analyses of the hemodynamic results were only performed for patients that were successful in achieving LOC. Statistical significance was set at P < 0.05.

Results

The young, middle-aged, and elderly groups included 40 patients each. Hence, a total of 120 patients were analyzed (Fig. 1). The demographic characteristics of the patients are shown in Table 1. The characteristics were generally similar among the three groups, except for the mean age and ASA-PS score. The elderly group had a significantly higher percentage of patients with ASA-PS II, than the young and middle-aged groups. ASA-PS II comprised of 5, 40, and 70%, in the young, middle-aged, and elderly groups, respectively.

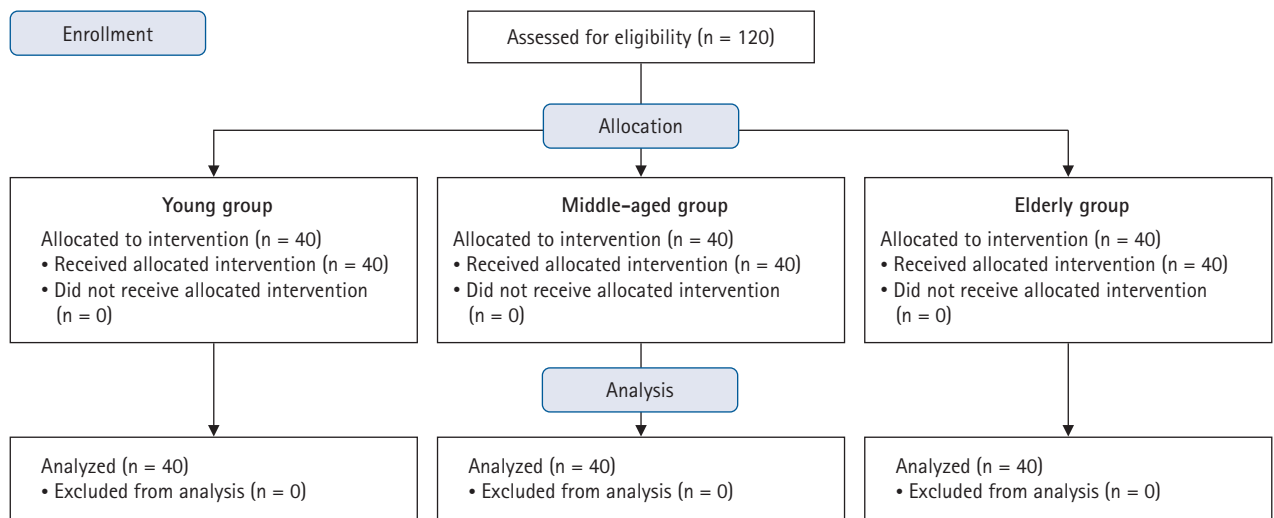


Fig. 1. CONSORT flow diagram of this study.

Table 1. Demographic Data

Parameters	Young group (n = 40)	Middle-aged group (n = 40)	Elderly group (n = 40)	P value
Age (yr)	29.5 ± 5.8	49.7 ± 5.4	66.6 ± 5.3	< 0.001
Sex (M/F)	19/21	24/16	18/22	0.356
Weight (kg)	68.1 ± 11.6	66.2 ± 11.6	64.7 ± 10.7	0.405
Height (cm)	166.8 ± 9.2	166.2 ± 8.3	161.8 ± 8.8	0.024
BMI	24.3 ± 2.5	23.8 ± 2.6	24.6 ± 2.8	0.376
ASA-PS				< 0.001
I	38 (95.0)	24 (60.0)	12 (30.0)	
II	2 (5.0)	16 (40.0)	28 (70.0)	

Values are presented as mean ± SD or number (%). BMI: body mass index, ASA-PS: American Society of Anesthesiologists physical status.

The sequences for success and failure of LOC during anesthesia induction by predetermined bolus dose of remimazolam are shown in Fig. 2 for each group according to the biased coin up-and-down method. The adjusted success rates from the PAVA are depicted in Fig. 3. The ED₉₅ of remimazolam required for LOC using isotonic regression was 0.367 mg/kg (95% CI [0.277, 0.392]) in the young group, 0.369 mg/kg (95% CI [0.266, 0.394]) in the middle-aged group, and 0.249 mg/kg (95% CI [0.199, 0.288]) in the elderly group (Table 2). The ED₉₅ values overlapped at the 95% CI level, resulting in no significant difference between the groups.

Intra-group analysis involved comparing each MAP at 1 and 3 min after administration with that at baseline. MAP decreased significantly compared to baseline throughout the 3-min study period in each group (Fig. 4A). HR in all three groups increased

at 1 min and 3 min after administration, compared to baseline values (Fig. 4B). During the 3-min of this study, none of the patients experienced hypotension or bradycardia that required rescue medications. Compared to baseline, BIS values at 1 and 3 min after administration were significantly reduced in all three groups, indicating adequate depth of anesthesia (Fig. 4C). BIS values at 3 min were 59.14 (\pm 7.25), 58.8 (\pm 7.91), and 59.92 (\pm 9.05) in the young, middle-aged, and elderly groups, respectively. No adverse events including injection pain were reported during the study period.

Discussion

Using the biased coin up-and-down method, we observed that

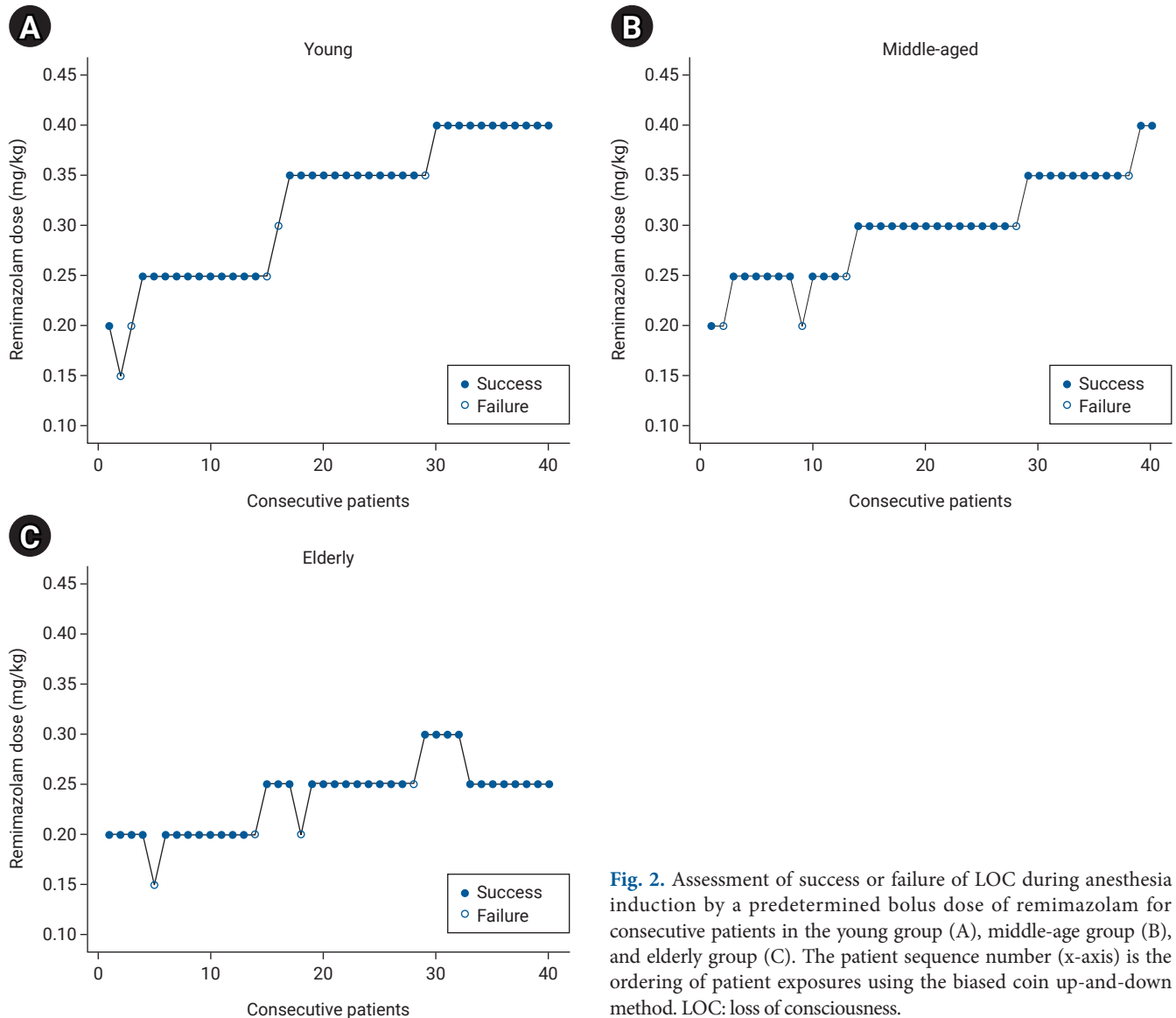


Fig. 2. Assessment of success or failure of LOC during anesthesia induction by a predetermined bolus dose of remimazolam for consecutive patients in the young group (A), middle-age group (B), and elderly group (C). The patient sequence number (x-axis) is the ordering of patient exposures using the biased coin up-and-down method. LOC: loss of consciousness.

Table 2. The ED₉₅ with 95% CI of Remimazolam for LOC Using Isotonic Regression in Each Group

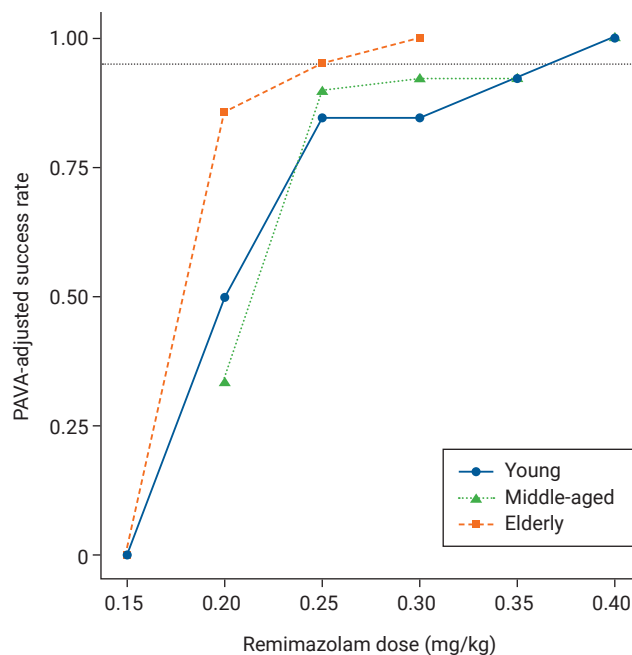
Group	Young (n = 40)	Middle-aged (n = 40)	Elderly (n = 40)
ED ₉₅ (mg/kg)	0.367	0.369	0.249
95% CI	0.277, 0.392	0.266, 0.394	0.199, 0.288

The ED₉₅ values overlapped at 95% CI. No significant differences were observed between the groups. ED₉₅: 95% effective dose, LOC: loss of consciousness.

the ED₉₅ of remimazolam required to achieve LOC was 0.367 mg/kg in the young group, 0.369 mg/kg in the middle-aged group and 0.249 mg/kg in the elderly group, demonstrating that the required dose of remimazolam was reduced in the old age group compared to the younger groups. However, the ED₉₅ values overlapped at the 95% CI, and the null hypothesis of equal effective doses was not rejected at an α value of 0.05. Remimazolam induction showed a trend of gradual decline in MAP and an increase in HR. However, MAP and HR were within the clinically normal range, and no patients required vasoactive medications. Consequently, the remimazolam used for induction did not cause significant hemodynamic depression.

In previous studies, continuous infusion of remimazolam for general anesthesia induction resulted in a statistically longer time to achieve LOC compared to single dose propofol induction. For example, a multicenter phase IIb/III trial revealed that the mean time to LOC in the continuous remimazolam 6 and 12 mg/kg/h groups were 102 and 88.7 s, respectively, whereas the propofol bolus group achieved LOC at 78.7 s, indicating that the propofol group had a shorter time to LOC [15]. This difference in onset time is thought to be caused by different methods of drug application. In practice, in the field of anesthesia, intravenous sedatives are usually administered as a single bolus dose to rapidly achieve high drug concentrations and then maintain adequate drug concentrations with subsequent continuous infusions [21]. That is why we sought to determine a single bolus dose of remimazolam to deliver the drug in a more practical, simple, and fast way. In this study, the time to achieve LOC when remimazolam was administered as a bolus was not measured, but it is likely to be faster than the time taken by the continuous infusion method in previous studies.

This study also evaluated the hemodynamic stability after single-bolus dose remimazolam induction in different age groups. In previous studies, the incidence of adverse events, such as hypotension, bradycardia, and low oxygen saturation, was significantly lower in the continuous remimazolam infusion group than in the propofol group [14,22,23]. Our study findings are consistent with those of previous studies as bolus administration of remimazolam

**Fig. 3.** PAVA-adjusted success rate according to dose level in each group. PAVA: pooled adjacent violators algorithm.

did not induce hypotension or bradycardia across various age groups. As described above, although remimazolam induces less hypotension than propofol, a recent study reports that the incidence of hypotension increases as the dose of remimazolam increases [17]. This result justifies our study findings as selecting an appropriate dose considering other requirements, such as age, can reduce the possibility of hypotension. Therefore, we conclude that a single dose of remimazolam after precise dosing of the ED₉₅ value can help maintain hemodynamic stability, even in elderly patients. Regarding the effect of remimazolam on HR, although previous studies have consistently shown that remimazolam is much less likely to cause bradycardia than propofol, the pattern of HR changes over time with remimazolam has not been clearly documented [14,17,22,23]. In this 3-min study conducted after remimazolam bolus without other anesthetics, remimazolam did not cause severe tachycardia, but HR significantly increased compared to that at baseline in all groups. Therefore, sufficient attention is required for the increase in HR caused by remimazolam.

In general, the estimation of the dose for new agents is aimed at the minimum dose, which provides a 50% probability of response (effective dose 50, ED₅₀). The Dixon and Mood up-and-down method that targets the ED₅₀ is commonly used for dose-finding studies of fast response drugs such as anesthetics [19,24]. In a previous study, the estimation of the remimazolam dose to achieve LOC was a mean dose [15]. However, it is important to identify the ED₉₅ to determine the dose of drugs for anesthesia [24], as

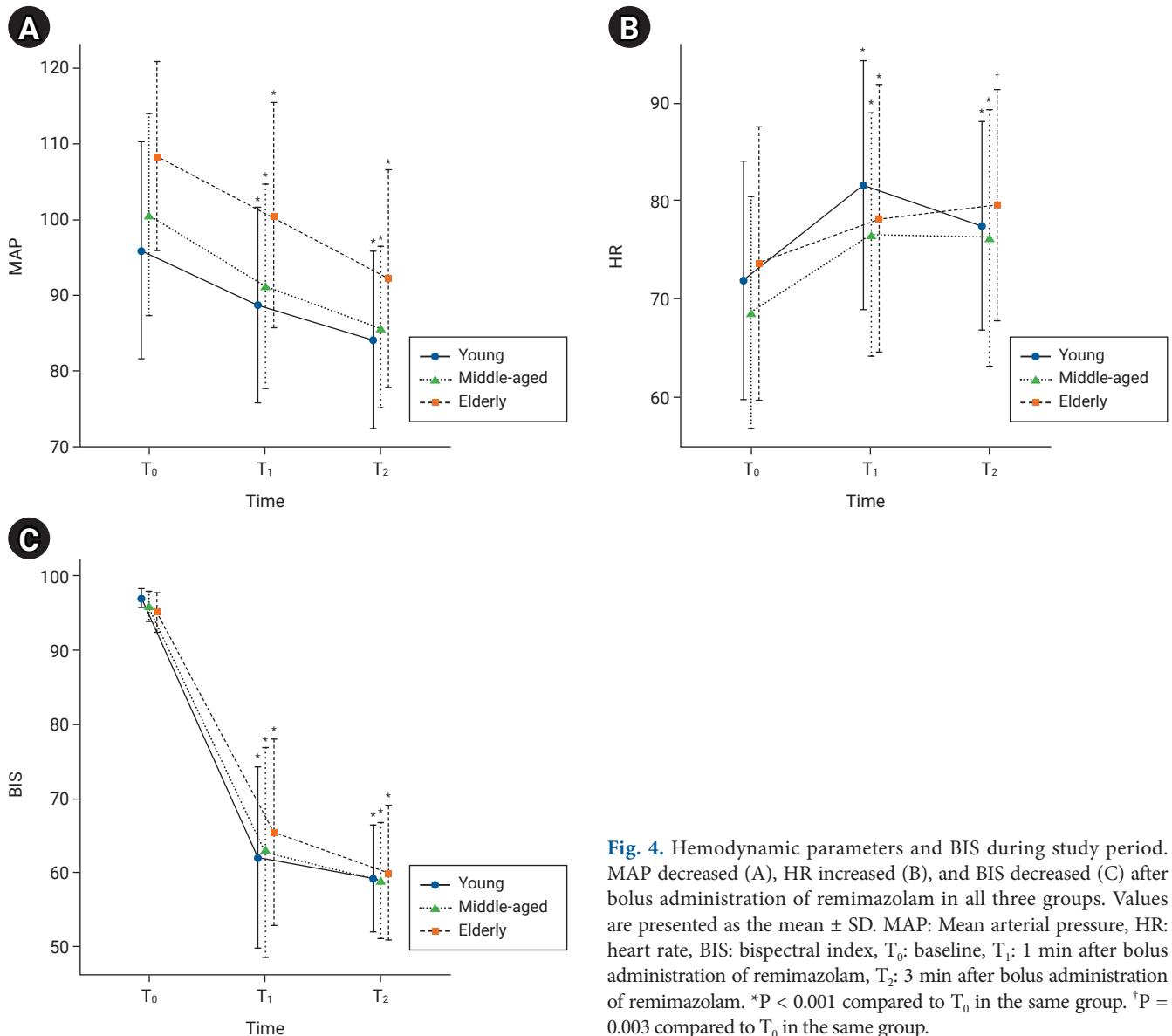


Fig. 4. Hemodynamic parameters and BIS during study period. MAP decreased (A), HR increased (B), and BIS decreased (C) after bolus administration of remimazolam in all three groups. Values are presented as the mean \pm SD. MAP: Mean arterial pressure, HR: heart rate, BIS: bispectral index, T₀: baseline, T₁: 1 min after bolus administration of remimazolam, T₂: 3 min after bolus administration of remimazolam. *P < 0.001 compared to T₀ in the same group. †P = 0.003 compared to T₀ in the same group.

50% efficacy is an inappropriately low threshold for anesthesia. The biased coin up-and-down method generalized the Dixon and Mood up-and-down method as it finds ED values for other quantiles using modifications to the dose assignment rule and is commonly utilized for calculating the ED₉₅ of anesthetics. To determine a dose such as the ED₉₅, the biased coin uses a probability of 1/19 (\approx 0.05). In this method, the doses are allocated sequentially based on the responses of the previous patient. In detail, doses are increased after an identification of negative response (failure of LOC), indicating that the current dose is not sufficient. However, following a positive response (success of LOC), the next patient is randomized with a probability of 0.05 to the next lower dose and with a probability of 0.95 to the same dose. Examples of the biased coin up-and-down method in anesthesia to find an ED₉₅ dose can

be found in numerous studies [25–29]. Therefore, we used this method to investigate the ED₉₅ of remimazolam.

As life expectancy is increasing globally, the proportion of elderly individuals requiring surgery is also increasing. Elderly patients scheduled for surgery pose a challenge as anesthesiologists frequently need to titrate anesthetic drug doses to account for the physiology of older individuals. These concerns are valid for all anesthetic drugs, and a phase I study, ONO-2745-01, conducted in Japan evaluated the pharmacokinetics and pharmacodynamics of an intravenous bolus of remimazolam in young adults (aged 20–45 years) and elderly individuals (aged 65–74 years) [30]. No difference in pharmacokinetics was observed between the young and elderly groups, but a small pharmacodynamic effect related to increased age was identified (i.e., shorter onset of LOC and longer

duration of sedation in the elderly group). In this study, we used elderly patients to determine the ED₉₅ of remimazolam for induction and found that the results showed a decreasing trend in elderly patients.

This study had several limitations. First, the study was designed to evaluate the success and failure of LOC for only 3 min after remimazolam administration without any additional anesthetics, such as opioids or neuromuscular blocking agents. Therefore, the interaction of remimazolam with other anesthetic agents, as well as the hemodynamic stability after 3 min, was not evaluated. Second, we enrolled relatively healthy patients (ASA-PS I and II). Patients with severe comorbidities may exhibit different sensitivities to remimazolam; therefore, subsequent studies are required to confirm the safety and efficacy of remimazolam in such patients. Third, we used the biased coin up-and-down method to select the sample size, and 40 patients was the minimum number required. Although our results were consistent with those of previous studies, we suggest that studies involving larger cohorts will help to determine a more accurate dose of the ED₉₅.

In conclusion, the ED₉₅ of remimazolam bolus for LOC in general anesthesia was 0.367 mg/kg in the young group, 0.369 mg/kg in the middle-aged group and 0.249 mg/kg in the elderly group. In all patients in this study, hemodynamic stability was maintained with a bolus administration of remimazolam, and no injection site pain was observed. Therefore, in clinical practice, titration of remimazolam bolus according to age is recommended, and further studies are needed on the interaction of remimazolam with other anesthetics.

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Conflicts of Interest

Sung Yong Park has been an editor for the Korean Journal of Anesthesiology since 2016. However, he was not involved in any process of review for this article, including peer reviewer selection, evaluation, or decision-making. There were no other potential conflicts of interest relevant to this article.

Author Contributions

Juyeon Oh (Data curation; Investigation; Resources; Writing – original draft; Writing – review & editing)
Sung Yong Park (Conceptualization; Data curation; Funding ac-

quisition; Investigation; Methodology; Writing – original draft; Writing – review & editing)

Sook Young Lee (Writing – review & editing)

Ju Yeol Song (Data curation; Investigation)

Ga Yun Lee (Data curation; Resources)

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