Drug Design, Development and Therapy Dovepress

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Effect-Site Concentration of Remimazolam by Age Groups During Target-Controlled Infusion for Total Intravenous Anesthesia: A Retrospective Comparative Study

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Purpose: Pharmacokinetic and pharmacodynamic (PKPD) models exist for remimazolam, but data for target-controlled infusion (TCI) are limited. The Schüttler PKPD model, a three-compartment model including body weight as a covariate, does not account for age as a variable. This study aimed to investigate remimazolam's effect-site concentration (Ce) in different age groups during sedation and general anesthesia with TCI using Schüttler PKPD model.

Patients and methods: Records of patients who underwent remimazolam TCI with the Schüttler model were reviewed. During anesthesia induction, the target Ce of remimazolam was gradually increased until loss of responsiveness, and it was titrated to maintain bispectral index of 40–70 during operation. Patients were categorized into young (20–40 years, n=24), middle-aged (41–60 years, n=27), and elderly (61–80 years, n=35) groups. Bispectral index and hemodynamic variables were also assessed.

Results: The elderly group had significantly lower remimazolam Ce compared to the young and middle-aged groups at all sedation levels, intubation, and surgery. Mean highest intraoperative Ce was 0.78±0.10, 0.71±0.07, and 0.61±0.10 μg/mL in young, middle-aged, and elderly groups, respectively (P<0.001). The recovery of responsiveness during emergence occurred at significantly lower Ce in the elderly group (0.28±0.06 μg/mL) than in the young (0.41±0.07 μg/mL) and middle-aged groups (0.35±0.07 μg/mL, P<0.001). Ce during sedation and general anesthesia was comparable between the young and middle-aged groups. The bispectral index was similar across groups but fluctuated more in the elderly group during general anesthesia. Elderly patients also showed the greatest systolic blood pressure suppression (18.4 ± 13.29% before intubation and 34.31 ± 14.91% during surgery).

Conclusion: Older patients may require lower target Ce during remimazolam TCI for sedation and anesthesia, with emergence occurring at lower Ce. Blood pressure suppression may be greater in elderly patients under deep sedation or general anesthesia.

Keywords: remimazolam, pharmacology, anesthesia, general, sedation, elderly

Introduction

Remimazolam, a novel ultra-short-acting benzodiazepine, has been developed for anesthesia induction and maintenance, facilitating total intravenous anesthesia (TIVA).[1] While propofol has traditionally served as the primary hypnotic agent in TIVA, its use is associated with adverse effects such as hemodynamic suppression and injection pain.[2] Remimazolam has been reported to induce fewer hemodynamic effects; however, similar to other anesthetics, the pharmacodynamics of remimazolam may be influenced by age.[3] Previous studies have demonstrated that older patients require lower doses for sedation and maintenance of anesthesia than young patients.[4,5]

Sedatives and opioids commonly used in TIVA, such as propofol and remifentanil, have a narrow therapeutic window and rapid onset and offset; therefore, they are administered via target-controlled infusion (TCI) using predicted effect-site

Received: 31 May 2024
Accepted: 8 November 2024
Published: 12 November 2024

concentrations (Ce). Ce represents the effectiveness of anesthetics and can be used as a reference to predict their pharmacodynamic effects. With the recent development of pharmacokinetic-pharmacodynamic (PKPD) models for remimazolam,[5–7] TCI based on predicted Ce has become feasible. The Schüttler model, a three-compartment model, incorporates body weight as a covariate, significantly influencing the volume of distribution in the central compartment.[7] Consequently, even when administered at the same dose based on body weight, Ce of remimazolam may differ among individuals. Our previous study using the Schüttler model revealed that age was negatively correlated with Ce at deep sedation and recovery of responsiveness in patients undergoing TCI using the Schüttler model.[8] However, studies on the clinical application of TCI are still limited, and the adjustment of target Ce values according to age during TCI for sedation and anesthesia remains unclear.

Remimazolam administration has been associated with adverse reactions, including hypotension, bradycardia, decreased oxygen saturation, dizziness, nausea, and prolonged sedation.[1] Older patients may have an increased sensitivity to remimazolam, which may increase their susceptibility to adverse effects compared to younger adults. However, few comparative studies have explored hemodynamic changes across different age groups in patients receiving remimazolam. Therefore, determining age-related differences in hemodynamic changes during remimazolam TIVA is essential.

In this study, we retrospectively analyzed data from patients undergoing remimazolam TCI to compare the predicted Ce at different sedation levels during general anesthesia and recovery from anesthesia, according to age groups. We also aimed to compare changes in bispectral index (BIS) and hemodynamic variables. We hypothesized that the remimazolam Ce during sedation or TIVA would be lower, and hemodynamic changes would be greater in older patients (age >60 years) than in younger patients.

Methods

This was a retrospective study involving patients who underwent elective surgery under TIVA using TCI of remimazolam Ce between September 2022 and July 2023 at the Catholic University Yeouido St. Mary's Hospital, a secondary care teaching hospital in Seoul, Korea. The Institutional Review Board (IRB) of the Catholic University of Korea, Yeouido St. Mary's Hospital, approved the study protocol (approval number: SC23RISI0226), which was registered with the Clinical Research Information Service of the Korea National Institute of Health (CRIS, http://cris.nih.go.kr, identification number: KCT0009171). The IRB of the Catholic University of Korea, Yeouido St. Mary's Hospital approved a waiver of informed consent because the data were handled in a completely anonymous manner, which minimizes the risk to patients and aligns with ethical guidelines for retrospective studies. All patient data were managed in a de-identified and anonymous format, ensuring that no personal identifiers were linked to the medical records, in compliance with the IRB's policies on data confidentiality and privacy protection. This study was conducted in accordance with the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statements.

Selection Criteria

The medical records of patients aged 20–80 years who underwent remimazolam TIVA with remifentanil infusion for elective surgery (duration <2h) were retrospectively reviewed. The study included patients who underwent remimazolam TCI using the Schüttler model for anesthesia induction and maintenance, with continuous recording of the predicted Ce of remimazolam and BIS. The exclusion criteria were as follows: patients who received other inhalation anesthetics or intravenous sedatives during anesthesia, those whose dosage of remimazolam or remifentanil was unclear, and those with missing data.

Anesthesia Protocol

Patients fasted for >8h before surgery and did not receive premedication. Upon arrival in the operating room, the patient's electrocardiogram, peripheral oxygen saturation (SpO_2), and noninvasive arterial blood pressure (BP) were monitored and recorded every 5 min throughout the entire procedure. BIS (BIS® monitor, Covidien Medical, Boulder, CO, USA) was monitored and continuously recorded using vital sign recorder software (VitalDB, https://vitaldb.net).

Anesthesia was induced with remimazolam (Byfavo™ Inj; Hana Pharm Co., Ltd., Hwaseong, South Korea) using a TCI syringe pump (Pion pump, Bionet Co. Ltd., Seoul, Korea) that was controlled by TCI software (Asan pump, version 2.1.5,

Bionet Co Ltd.) programmed with the PKPD model reported by Schüttler et al.[7] The plasma effect-site equilibration rate constant (k_{e0}) for the Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S scale) was used, which is 0.27 (min^{-1}).[7] The remimazolam Ce was predicted by Asan pump software and initially targeted 0.25 or 0.3 μg/mL. When the predicted Ce of remimazolam was reached the targeted concentration, the BIS and sedation levels were recorded. The level of sedation was assessed using the responsiveness component of the MOAA/S scale (0= does not respond to deep stimulus; 1= does not respond to mild prodding or shaking; 2= responds only after mild prodding or shaking; 3= responds only after name is called loudly or repeatedly; 4= lethargic response to name spoken in normal tone; 5= responds readily to name spoken in normal tone).[9] Remimazolam Ce was increased sequentially by 0.05 μg/mL until the sedation level reached MOAA/S scale 1. After the sedation level reached MOAA/S scale 1, a continuous infusion of remifentanil (0.2–0.3 μg/kg/min) was started. The target Ce was increased by 0.05–1 μg/mL from Ce at MOAA/S 1, and rocuronium 0.6 mg/kg was administered to facilitate endotracheal intubation. After endotracheal intubation, the target Ce of remimazolam and the infusion rate of remifentanil were titrated to maintain a BIS of 40–70 and a heart rate change within 20% of baseline.

Approximately 5 min before the end of surgery, the target Ce of remimazolam and the infusion rate of remifentanil were reduced by 20–30%, and the infusion of anesthetics was stopped at the end of surgery. Sugammadex 2 mg/kg was administered to reverse neuromuscular blockade. Ce of remimazolam was recorded when patients opened their eyes after verbal stimulation or mild shaking (defined as recovery of response [ROR]) and endotracheal extubation. If the patient did not wake up within 15 min after the discontinuation of remimazolam or if self-respiration was depressed after endotracheal extubation, 0.2 mg of intravenous flumazenil was repeated.

Hemodynamic variables were recorded in the electronic anesthesia record of our institution, and the predicted Ce was continuously recorded using Asan pump software. Ce at each sedation level and emergence from anesthesia were recorded in the VitalDB files.

Variables and Outcome Measurements

The study population was stratified into three groups: young (20–40 years old), middle-aged (41–60 years old), and elderly (61–80 years old). Data was retrospectively collected from electronic medical/anesthesia records, including sex, age, American society of anesthesiologists physical status classification (ASA class), underlying medical conditions, body weight, height, duration of surgery and anesthesia, total dose of remimazolam (mg), total dose of remifentanil (μg) systolic and diastolic blood pressure (SBP and DBP), and heart rate (HR) during anesthesia. Hemodynamic variables were recorded at 5-min intervals. Remimazolam infusion data were automatically stored in Excel files using the Asan Pump program after completion of each case. BIS data were extracted from vital DB files and saved as Excel files (Microsoft Corporation, Redmond, WA, USA) at 10-second intervals. To analyze BIS changes, the highest and lowest BIS and 95% spectral edge frequency (SEF 95) during the operation were checked, and the difference between these two values was calculated for each patient. We investigated each patient's BIS during the operation and checked for those with a BIS exceeding 70 for more than one minute. Additionally, changes in hemodynamic parameters were assessed by identifying the highest and lowest intraoperative SBP in each patient's record and calculating the percent change from the baseline SBP. The percent change from baseline was calculated as the difference in SBP from baseline divided by the baseline SBP multiplied by 100 (%). Hypertension was defined as SBP >160 mmHg, whereas hypotension was defined as SBP <90 mmHg. We checked the incidence of hypertension and hypotension, as well as the number of patients receiving nicardipine, ephedrine, or atropine.

This study aimed to compare remimazolam Ce among three groups at different levels of sedation (MOAA/S 1–5), during the operation, and during emergence from anesthesia.

The secondary objective was to analyze the changes in BIS and hemodynamic variables.

Statistical Analysis

The sample size was calculated assuming the following variables: It was determined that a minimum of 20 subjects per group should be included if we calculate the number of subjects to detect a difference in mean and standard error of Ce at MOAA/S 1 between groups of 0.1 and 0.08, respectively. When data collection was completed, the groups included 24, 27, and 35 patients, respectively. With this sample size, the significance level was 5%, and the power was over 95%.

Statistical analyses were performed using SPSS (version 24.0; SPSS Inc., Chicago, IL, USA) for Windows (Microsoft Corporation, Redmond, WA, USA). To compare the three groups, we presented numerical variables as means and standard deviations and categorical data as counts and percentages. Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test. For normally distributed data, statistical analysis was performed using a one-way analysis of variance, followed by a Bonferroni or Tukey post-hoc test. For non-normally distributed data, statistical analysis was performed using the Kruskal–Wallis test, followed by the Mann–Whitney *U*-test with a Bonferroni correction for significance level (corrected P=0.017). Data that were not normally distributed included the duration of surgery and anesthesia, remimazolam dose, remifentanil dose, Ce at intubation, BIS at extubation, BIS ROR, and percentage (%) increase in SBP from baseline when the intraoperative SBP was highest. The incidence of categorical data was analyzed using the chi-square test or Fisher's exact test. After comparing the three groups, the two groups were compared again when a significant difference was observed. P<0.05 were considered statistically significant.

Results

During the study period, 95 patients underwent remimazolam TCI, four of whom were converted to inhalation anesthesia during surgery, and five were excluded because of missing data, resulting in a total of 86 patients (24, 27, and 35 in the young, middle-aged, and elderly groups, respectively) whose data were included (Figure 1). The patients underwent minimally invasive surgeries, including cholecystectomy (n=49), transurethral resection of the bladder or prostate (n=12), hysteroscopy (n=10), and other procedures (tension-free vaginal tape obturator procedure, loop electrosurgical excision procedure, closed reduction, internal fixation, etc).

Table 1 shows the patients' demographic and perioperative data. In the elderly group, the proportion of male patients (P=0.039 vs young group), ASA class III patients (P<0.001 vs young group and P=0.002 vs middle-aged group), hypertensive patients (P<0.001 vs young and middle-aged groups), and diabetic patients (P<0.001 vs young group and P=0.041 vs middle-aged group) were significantly higher than those in the young or middle-aged groups. The duration of surgery and anesthesia showed significant differences in the Kruskal–Wallis test; however, post hoc tests showed that only the duration of anesthesia was significantly different between the young and elderly groups (P=0.006). The remimazolam and remifentanil infusion rates were significantly lower in the elderly group compared to the young group (all $P < 0.001$).

Table 2 presents the remimazolam Ce and BIS at different sedation levels. The elderly group had significantly lower Ce values at all sedation levels compared to the young and middle-aged groups (all P<0.001 for the elderly vs young or

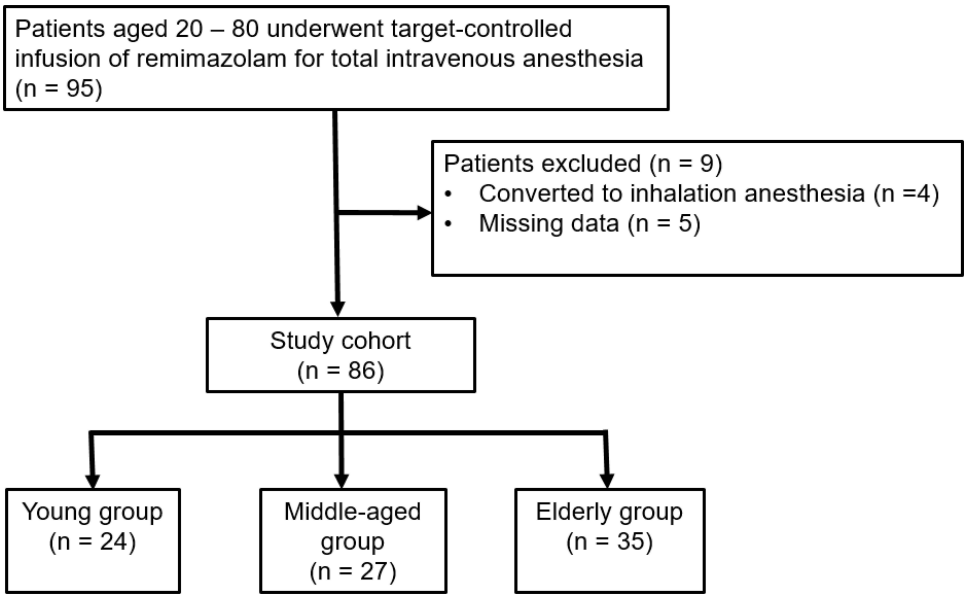

Figure 1 Flow chart of the study.

Table 1 Demographic and Perioperative Data of the Patients

Variables	Young Group (n = 24)	Middle-Aged Group (n = 27)	Elderly Group (n = 35)	*P*
Age (years)	30.50±6.23†	50.96±6.32*†	70.63±5.58*	<0.000
Sex (male/female)	7/17	10/17	21/14	0.043
ASA classification (I/II/III)	18/6/0	9/16/2	1/25/9	<0.001
Hypertension	1	5	27	<0.001
Diabetes mellitus	0	3	12	0.002
Height (cm)	165.90±7.91	163.90±9.39	162.21±8.48	0.276
Body weight (kg)	63.48±12.88	66.35±14.01	63.52±9.90	0.603
BMI (kg/m^2)	22.95±3.78	24.51±3.51	24.09±2.98	0.243
Duration of operation (min)	31.25±11.33	33.81±20.15	43.06±21.88	0.042
Duration of anesthesia (min)	55.63±12.54†	61.11±21.98†	72.4±24.16*	0.012
Remimazolam dose (mg)	59.98±12.80	59.06±17.38	58.98±18.24	0.856
Remifentanil dose (μg)	652.5±212.22	650.74±243.38	635.66±239.86	0.953
Remimazolam infusion rate (mg/kg/h)	1.08±0.28†	0.93±0.24	0.8±0.15*	<0.001
Remifentanil infusion rate (μg/kg/min)	0.19±0.05†	0.16±0.04	0.14±0.04*	0.001

Notes: Data are presented in mean ± SD or number. Young group: 20–40 yr-old patients, middle-aged group: 41–60 yr-old patients, elderly group: 61–80 yr-old patients. Infusion rate: total dose/weight/anesthesia duration *P < 0.05 versus young group, †P < 0.05 versus elderly group.
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index.

Table 2 Effect Site Concentration of Remimazolam and Bispectral Index at Each Level of Sedation in the Three Age Groups

	Remimazolam Ce (μg/mL)			Bispectral Index		
	Young Group	Middle-Aged Group	Elderly Group	Young Group	Middle-Aged Group	Elderly Group
MOAA/S 4	0.39±0.07†	0.38±0.07†	0.32±0.05*	79.56±4.23	81.26±5.25	80.57±4.71
MOAA/S 3	0.48±0.06†	0.46±0.05†	0.41±0.07*	72.97±5.38†	73.16±4.30	75.51±4.64*
MOAA/S 2	0.59±0.10†	0.56±0.07†	0.47±0.07*	67.37±5.21†	66.94±4.35†	70.46±4.57*
MOAA/S 1	0.68±0.09†	0.64±0.06†	0.54±0.07*	61.63±4.99	61.89±4.42	63.90±6.02

Notes: Data are presented in mean ± SD. Young group: 20–40 yr-old patients, middle-aged group: 41–60 yr-old patients, elderly group: 61–80 yr-old patients. *P < 0.05 versus young group, †P < 0.05 versus elderly group.
Abbreviations: Ce, effect site concentration; MOAA/S, Modified Observer's Assessment of Alertness/Sedation scale.

middle-aged groups). BIS values were comparable among the groups at MOAA/S levels 4 and 1, but were significantly higher in the elderly group at MOAA/S levels 2 and 3 compared to the young and middle-aged groups (MOAA/S 2: *P*=0.047 vs young group; MOAA/S3: *P*=0.001 and <0.001 vs young and middle-aged groups, respectively). The distribution of bispectral index or MOAA/S scale according to remimazolam Ce is presented in Supplementary Figures 1 and 2.

During general anesthesia, Ce was lower in the elderly group than in the younger group. Ce at intubation and peak Ce during surgery were significantly lower in the elderly group than in the other groups (all *P* <0.001 in the elderly vs young or middle-aged groups; Table 3). During emergence from anesthesia, Ce at extubation and ROR were significantly lower in the young to elderly groups (Ce at ROR: P=0.004, <0.001, and 0.001; Ce at extubation: P=0.002, <0.001, and 0.008 in the young vs middle-aged, young vs elderly, and middle-aged vs elderly groups, respectively).

The BIS at intubation and emergence from anesthesia were comparable among the three groups (Table 3). The lowest BIS during surgery was significantly higher in the young group than in the other groups (all *P*<0.001); therefore, the young group had the smallest changes in BIS during surgery (*P*=0.034 and <0.001 for the young vs middle-aged and elderly groups, respectively). Approximately 20.8%, 11.1%, and 5.7% of patients in the young, middle-aged, and elderly groups, respectively, showed a BIS >70 for >1 min during surgery. Both the lowest and highest SEF 95 were significantly

Table 3 Intraoperative Data by Age Groups

	Young Group (n = 24)	Middle-Aged Group (n = 27)	Elderly Group (n = 35)	*P*
At intubation				
Ce (μg/mL)	0.72±0.09†	0.70±0.07†	0.58±0.07*	<0.001
BIS	60.38±6.54	58.56±6.36	58.14±6.33	0.782
During operation				
Peak Ce (μg/mL)	0.78±0.10†	0.71±0.07†	0.61±0.10*	<0.001
Highest BIS	69.84±5.79	66.57±4.64	66.56±6.30	0.062
Lowest BIS	47.38±4.86†	40.16±6.91*	37.56±4.92*	<0.001
BIS difference	21.42±6.22†	26.41±5.86*	29.00±7.93*	<0.001
BIS >70 for > 1 min (n = 10, 11.1%)	5 (20.80%)	3 (11.10%)	2 (5.7%)	0.204
Lowest SEF95	16.28±1.51†	15.04±1.47*	14.62±1.55*	<0.001
Highest SEF95	21.92±2.04†	20.23±2.35*	20.69±2.23*	0.005
During Emergence				
Ce at ROR (μg/mL)	0.41±0.07†	0.35±0.07*†	0.28±0.06*	<0.001
BIS at ROR	79.92±4.47	79.30±5.33	79.54±5.27	0.886
Ce at extubation (μg/mL)	0.39±0.07†	0.33±0.07*†	0.28±0.05*	<0.001
BIS at extubation	80.42±4.90	80.00±4.67	80.48±5.08	0.922
ROR after extubation (n)	3 (12.5%)	5 (18.5%)	14 (40%)	0.035
Flumazenil (n)	0	1 (3.70%)	4 (11.42%)	0.156

Notes: Data are presented in mean ± SD or number. Young group: 20–40 yr-old patients, middle-aged group: 41–60 yr-old patients, elderly group: 61–80 yr-old patients. *P < 0.05 versus young group, †P < 0.05 versus elderly group.
Abbreviations: Ce, effect-site concentration of remimazolam; BIS, bispectral index; BIS difference, difference of highest and lowest BIS during operation; SEF95, 95% spectral edge frequency; ROR, recovery of responsiveness.

higher in the young group than in the middle-aged and elderly groups (lowest SEF 95: *P*=0.014 and <0.001; highest SEF 95: *P*=0.017 and 0.009 in the young vs middle-aged and elderly groups, respectively).

Most patients recovered responsiveness before extubation, with a difference in Ce at ROR and extubation of approximately 0.02 μg/mL in the young and middle-aged groups. In the elderly group, 40% showed ROR after extubation, resulting in similar Ce values at ROR and extubation (*P*=0.041; Table 3). Flumazenil was administered to one patient in the middle-aged group and four in the elderly group, with two elderly patients requiring it after extubation due to decreased respiration and re-sedation.

Table 4 and Figure 2 show the hemodynamic changes during anesthesia. Baseline BP was significantly higher in the middle-aged (*P*=0.022 and 0.032 for SBP and DBP, respectively) and elderly (*P*<0.001 and 0.030 for SBP and DBP,

Table 4 Hemodynamic Variables During Anesthesia

	Young Group (n = 24)	Middle-Aged Group (n = 27)	Elderly Group (n = 35)	*P*
Baseline SBP (mmHg)	130.04±14.16†	145.63±22.36*	155.11±21.92*	<0.001
Baseline DBP (mmHg)	77.42±9.93†	85.63±13.21*	85.23±10.31*	0.015
Baseline HR (beat/min)	72.58±12.06	74.81±12.94†	66.20±12.81	0.024
SBP before intubation (mmHg)	119.04±9.83	128.74±17.22	125.31±21.97	0.152
DBP before intubation (mmHg)	69.38±8.56†	81.56±11.61*	75.97±9.87*	<0.001
HR before intubation (beat/min)	70.33±13.59	74.74±13.79	67.43±12.19	0.099
SBP after intubation (mmHg)	129.33±18.85†	147.11±23.40*	149.83±24.81*	0.003
DBP after intubation (mmHg)	77.75±21.14	88.11±15.37	86.80±17.37	0.086
HR after intubation (beat/min)	73.50±13.13	78.78±17.85	71.17±12.01	0.120
Lowest SBP during operation (mmHg)	109.21±8.59†	107.63±15.50	99.66±16.25*	0.023
Highest SBP during operation (mmHg)	135.5±16.75†	151±18.33*	158.6±22.99*	<0.001

Notes: Data are presented in mean ± SD. Young group: 20–40 yr-old patients, middle-aged group: 41–60 yr-old patients, elderly group: 61–80 yr-old patients. *P < 0.05 versus young group, †P < 0.05 versus elderly group.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

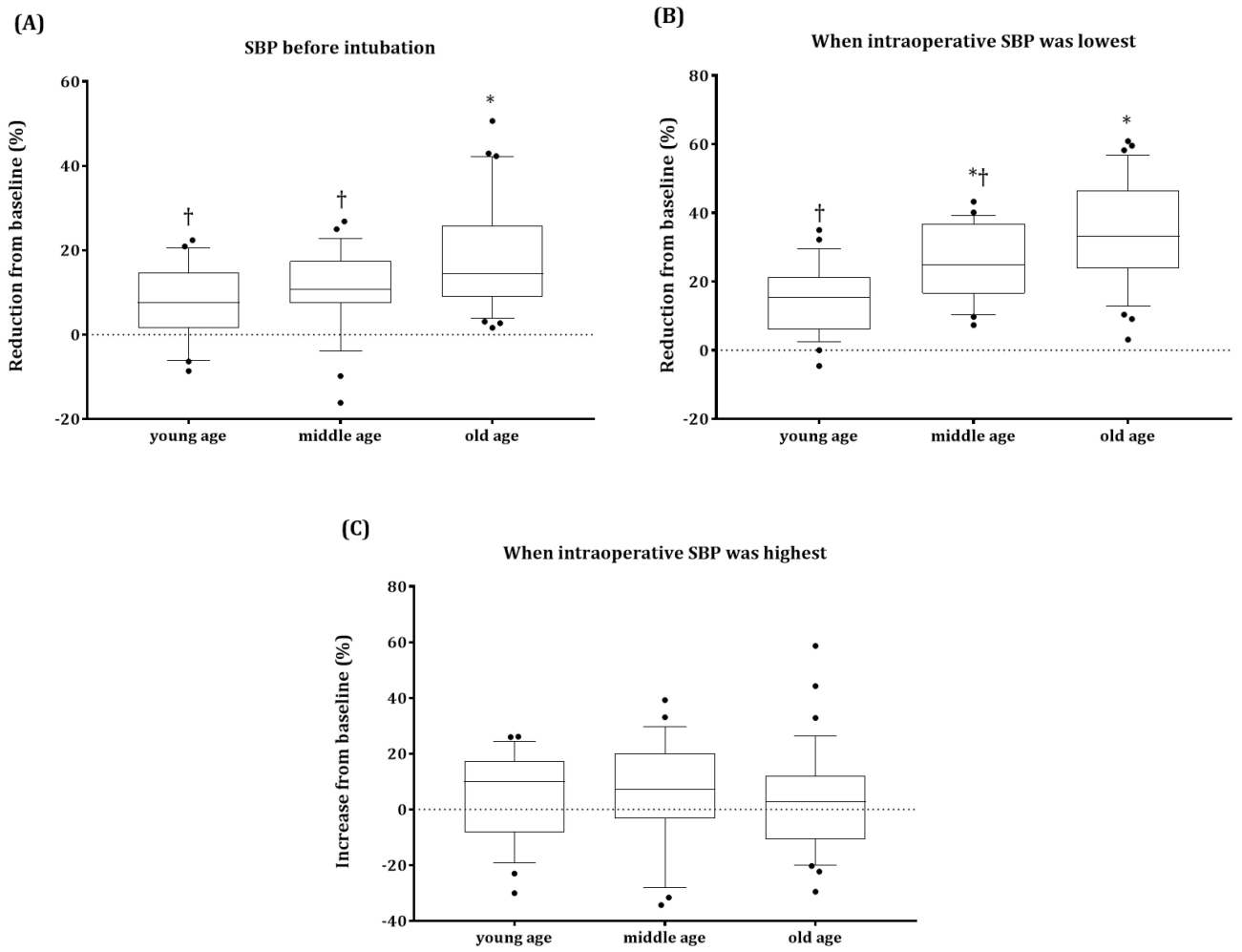

Figure 2 Percentage changes of systolic blood pressure compared to baseline. Boxplot represent the median, as well as the 25% and 75% interquartile range. The upper and lower notches indicate the 90th and 10th percentiles of the sample. Values below and above the notches are drawn as individual points. (**A**) Percentage (%) decrease in SBP from baseline before intubation. *P < 0.05 versus young group, †P < 0.05 versus elderly group. (**B**) Percentage (%) decrease in SBP from baseline when intraoperative SBP was lowest. **P* < 0.05 versus young group, †*P* < 0.05 versus elderly group. (**C**) Percentage (%) increase in SBP from baseline when intraoperative SBP was highest.
Abbreviation: SBP, systolic blood pressure.

respectively) groups than in the young group (Table 4). Before intubation, the elderly group experienced a greater drop in SBP (18.4 ± 13.29%) compared to the young (7.84 ± 8.74%, *P*=0.002) and middle-aged groups (10.85 ± 9.90%, *P*=0.026, Figure 2A). After intubation, the SBP was significantly higher in the middle-aged (*P*=0.021) and elderly (*P*=0.003) groups than in the young group (Table 4). The lowest intraoperative SBP was significantly lower in the elderly group than in the young group (*P*=0.041). When intraoperative SBP was lowest, it decreased by 15.21 ± 10.02%, 25.27 ± 10.42%, and 34.31 ± 14.91% in the young, middle-aged, and elderly groups, respectively, with a significantly greater decrease in the elderly groups (*P*=0.014, <0.001, and 0.016 in the young vs middle-aged, young vs elderly, and middle-aged vs elderly groups, respectively; Figure 2B). When intraoperative SBP was highest, SBP was significantly higher in the middle-aged (*P*=0.019) and elderly (*P*<0.001) groups than in the young group; the change from baseline was 5.20 ± 15.69%, 5.84 ± 18.87%, and 3.69 ± 18.45% in the young, middle-aged, and elderly groups, respectively, with no significant difference (*P*=0.886, Figure 2C).

Table 5 indicates that the incidence of intraoperative hypertension was significantly higher in the elderly (48.6%) and middle-aged (25.9%) groups compared to the young group (*P*<0.001 and 0.011 vs elderly and middle-aged groups, respectively). Hypotension was also more frequent in the elderly (25.7%) and middle-aged (11.1%) groups, and

Table 5 Side Effects and Administered Drugs During Anesthesia

Side Effects and Administered Drugs	Young Group (n = 24)	Middle-Aged Group (n = 27)	Elderly Group (n = 35)	*P*
Hypertension	0 (0%)	7 (25.9%)	17 (48.6%)	<0.001
Hypotension	0 (0%)	3 (11.1%)	9 (25.7%)	0.017
Nicardipine	2	2	10	0.038
Ephedrine	0	0	8	N/A
Atropine	0	1	1	N/A

Notes: Data are presented in number (percentage). Young group: 20–40 yr-old patients, middle-aged group: 41–60 yr-old patients, elderly group: 61–80 yr-old patients.

ephedrine was administered only in the elderly group. Nicardipine use was significantly more frequent in the elderly group compared to the younger groups.

Discussion

In this study, we compared Ce of remimazolam for each sedation level, anesthesia maintenance, and emergence from anesthesia according to the age group. Sedation was induced at a lower Ce in elderly patients than in younger patients; Ce during the maintenance of anesthesia and emergence from anesthesia was also lower. Elderly patients showed a more variable intraoperative BIS and a lower BIS than younger patients when the BIS was lowest during surgery. Changes in hemodynamic variables during anesthesia were greater in older patients.

Age can significantly influences the response to remimazolam administration.[3,4,10] Previous studies have shown that the effective dose of remimazolam for anesthesia induction is lower in elderly patients (age ≥ 60) compared to younger groups,[10] and that elderly patients experience faster onset of sedation, with a 75-year-old showing a 5–10-second quicker response than a 30-year-old at the same infusion rate.[3] Additionally, a case report demonstrated the successful use of approximately 1/5–1/10 of the recommended dose of remimazolam for maintenance of anesthesia in very elderly patients.[11] These findings highlight the need to adjust remimazolam dosages for elderly patients.

In the present study, the average Ce in the young and middle-aged groups was comparable at each level of sedation and induction of general anesthesia, but the average Ce in the elderly group was significantly lower at 0.32, 0.41, 0.47, and 0.54 at MOAA/S 4, 3, 2, and 1, respectively. In our previous study, remimazolam Ce associated with a 50% probability (Ce_{50}) of reaching MOAA/S scale 4, 3, 2, and 1, which were 0.30, 0.40, 0.48, and 0.65 g/mL, respectively, which was comparable to Ce in the young and middle-aged groups of the present study.[8] Although we could not incorporate age as a covariate for the pharmacodynamic model, we have reported that Ce at MOAA/S 1 and ROR were negatively correlated with age.[8] In the present study, we found that the elderly group had a lower Ce value and a narrower therapeutic range, with small differences between sedation levels. Ce at MOAA/S 1 was approximately 0.68 and 0.64 in the young and middle-aged groups, respectively, suggesting a need to reduce the target Ce by approximately 20% in elderly patients for deep sedation. The patient's age also influenced the target Ce for intubation and maintenance of anesthesia, with the elderly patient requiring a lower target Ce by 0.1–0.2 μg/mL compared to younger patients. These findings collectively suggest that elderly patients are more sensitive to the hypnotic effects of remimazolam, necessitating lower target Ce values for both induction and maintenance of anesthesia.

During emergence from anesthesia, the elderly group had delayed recovery compared to the other age groups, as ROR and extubation occurred at lower Ce values in this study. Ce at ROR was 0.41, 0.35, and 0.28 μg/mL in the young, middle-aged, and elderly groups, respectively. A retrospective simulation study using Schüttler's PKPD model estimated the median simulated Ce at ROR to be 0.3 μg/mL at a mean age of 56 years, and age was significantly correlated with simulated Ce at ROR.[12] In their pharmacodynamic model, the estimated Ce associated with a 50% probability of ROR was 0.52, 0.45, and 0.34 μg/mL in hypothetical patients aged 30, 50, and 80 years, respectively.[12] Their model had a high γ value of 32.3, and the difference in Ce and Ce values according to age was higher than the results of this study.

In the present study, ROR occurred first, followed by full recovery from respiration; therefore, Ce at extubation was lower than that at ROR in most patients. However, 40% of elderly patients experienced ROR after extubation, with no significant difference noted between the mean Ce at ROR and extubation. Although not statistically significant, the

elderly group had a higher incidence of flumazenil administration, with two patients requiring it due to respiratory depression after extubation. These findings align with a previous study that reported a higher likelihood of delayed extubation (≥15 minutes) in patients aged 79 years and older.[13] The results indicate that older patients may have narrower therapeutic ranges during both sedation and recovery. Therefore, the anesthetic regimen should be adjusted to account for age-related changes to optimize perioperative outcomes, and closer monitoring is recommended during emergence from remimazolam anesthesia for elderly patients.

It has been reported that processed electroencephalogram-derived indices, such as BIS and patient state index, are relatively high during remimazolam anesthesia.[14,15] Therefore, in the present study, we targeted a BIS of 40–70 during anesthesia. During sedation (MOAA/S 1–4), the BIS were similar among the three groups. However, during surgery, the young group had a higher BIS and less variation than the elderly group. The highest BIS was comparable, whereas the lowest BIS was significantly lower in the middle-aged and elderly groups than in the young group. It is possible that achieving deep anesthesia was easier in elderly and middle-aged patients despite the lower Ce, or that younger patients had relatively shallower anesthesia even with a higher Ce. Additionally, the middle-aged and elderly groups had lower SEF 95 values compared to the young group during surgery. Shirozu et al reported that SEF95 could be a supportive indicator for the depth of remimazolam anesthesia because BIS reached 60 or more in some cases during general anesthesia.[15] They reported a mean SEF95 of 15.3 ± 2.5 hz 30 minutes after the start of surgery, which was similar to our findings (lowest SEF95 during surgery).[15] However, the differences in BIS or SEF among different age groups during remimazolam anesthesia are unclear. During general anesthesia, the relationship between BIS and age is complex and may vary depending on the patient population and anesthetic. Previous studies on other anesthetics have shown that elderly patients may show higher BIS readings compared to younger patients at the same depth of anesthesia.[16,17] Yang et al reported that elderly patients had a higher BIS than younger patients when loss of consciousness was induced with propofol.[17] Another study found that older patients paradoxically exhibited higher BIS values despite receiving higher age-adjusted concentrations of inhalation anesthetics, suggesting that the BIS algorithm may be inaccurate in older adults.[16] Therefore, age-dependent BIS changes during remimazolam anesthesia still need to be further studied.

Remimazolam is known to be a lesser hemodynamic depressant than other anesthetics,[18,19] but it may lower BP during sedation and anesthesia. Chae et al reported that the effect of remimazolam on BP could be dose-dependent, while its effect on HR was inconclusive.[4] Schüttler et al found that high-dose continuous infusions of remimazolam produced a 10–34% decrease in BP from baseline in young male volunteers.[7] Another study in patients aged 45–80 years reported similar hemodynamic suppression between remimazolam and propofol during TIVA.[20] However, few studies have compared hemodynamic changes across age groups in patients undergoing remimazolam anesthesia.

In the present study, the elderly group had more patients with hypertension, resulting in a higher baseline BP, with an incidence similar to the estimated prevalence of 70–80% in populations over 65 years.[21] Hypertensive patients, even when treated, may exhibit greater hemodynamic instability during anesthesia than normotensive patients.[22] Before intubation, BP decreased by 7.85%, 10.85%, and 18.4% in the young, middle-aged, and elderly groups, respectively, with the elderly group showing the largest change. Intraoperative BP also decreased the most in the elderly group (34.31%). The incidence of intraoperative hypotension was relatively low (11.1% in middle-aged and 25.7% in elderly groups), while intraoperative hypertension was more common in the middle-aged (25.9%) and elderly (48.6%) groups. Choi et al reported that in hypertensive patients, the incidence of hypotension after induction with remimazolam was lower than with propofol, but the percent change in BP was similar (approximately 25%).[23] Therefore, while the frequency of hypotension with remimazolam may be lower, its severity can be greater in older hypertensive patients. These findings suggest that remimazolam may cause significant hemodynamic changes in elderly patients with hypertension, similar to other anesthetics. Therefore, anesthetic providers must closely monitor elderly patients with comorbidities for potential hemodynamic fluctuations during remimazolam TIVA.

This study had several limitations. First, it was a retrospective study. Demographic differences were observed between the groups. The elderly group had a smaller proportion of female patients and significantly more patients with diabetes, hypertension, and ASA class III. Previous studies have reported that female patients may have higher clearance rates and different infusion rates for the maintenance of anesthesia.[3,5] The infusion rate for maintaining anesthesia in ASA class III/IV patients has also been suggested to be lower than that in ASA class I/II patients.[6] Therefore, differences in these demographic

factors between groups may have biased the results. Second, we did not measure the plasma concentration of remimazolam and assumed that the PKPD model of Schuttler et al accurately predicted remimazolam Ce. True Ce may be more variable than that in the results of this study. Finally, the data from the present study cannot be assumed to be representative of the population. We included patients who underwent minimally invasive surgeries that took less than 2 h. Therefore, controlled studies with larger numbers of patients and more invasive or longer procedures are required. However, the present study provides reference values for future clinical applications of effect-site TCI during sedation, anesthesia maintenance, and recovery from general anesthesia according to age.

Conclusions

Older patients may require a lower target Ce during sedation and anesthesia with remimazolam TCI. Emergence from general anesthesia occurs at a lower predicted Ce in elderly patients. Changes in blood pressure during remimazolam anesthesia may be greater in elderly patients with hypertension.

Data Sharing Statement

The data supporting the study findings are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The protocol was approved by the Institutional Review Board (IRB) of the Catholic University of Korea, Yeouido St. Mary's Hospital, approved the study protocol (approval number: SC23RISI0226), and which was registered with on the Clinical Research Information Service of the Korea National Institute of Health (CRIS, http://cris.nih.go.kr, identification number: KCT0009171). Informed consent was waived because this was a retrospective study.

Author Contributions

All authors have made a substantial contribution to the work reported, be it in conception, design, execution, acquisition of data, analysis and interpretation, or all of these; have been involved in drafting, revising, or critically reviewing the article; have given final approval for the version to be published; have agreed on the journal to which the article will be submitted; and agree to take responsibility for all aspects of the work.

Funding

The authors wish to acknowledge the financial support of the Catholic Medical Center Research Foundation made in the program year of 2024.

Disclosure

The authors report no conflicts of interest in this work.

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