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Pharmacodynamic Modeling of Blood Pressure Reduction During Remimazolam Induction in Elderly Patients: A Modified Logistic Model with Body Weight as a Covariate

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ABSTRACT

Remimazolam is a newer hypnotic that generally preserves cardiovascular stability better than propofol during general anesthesia, a benefit that appears pronounced in older adults. Despite this, the extent to which remimazolam lowers blood pressure in a dose-related manner has not been formally quantified in this age group. We re-examined information from 432 individuals aged ≥ 65 years enrolled in a randomized trial comparing remimazolam with propofol for elective gastrectomy. Remimazolam was infused at a constant 6 mg/kg/h, whereas propofol was administered with a TCI system employing the Schnider model. Mean arterial pressure (MBP) values were expressed as fractional reductions relative to baseline. To relate cumulative remimazolam dose to MBP decline, we constructed a modified logistic regression model and assessed body weight as a potential influencing factor. Data from 209 participants per arm were suitable for evaluation. The customized logistic model reliably captured the dose–response pattern for MBP reduction produced by remimazolam, and model accuracy improved when body weight was included as a covariate. The remimazolam group showed a statistically larger MBP drop before intubation (28.0 ± 9.9% vs 25.8 ± 10.1%, P = 0.024), although the magnitude of this difference lacked practical clinical importance. In older patients receiving remimazolam for induction, the association between administered dose and MBP decrease was well represented by the modified logistic approach, with body weight exerting a meaningful influence. These findings imply that TCI-style dosing could help maintain more stable hemodynamics during induction. Clinical Research Information Service, KCT0006877, registered December 27, 2021.

Keywords: Remimazolam, Anesthesia, Hemodynamics, Aged, Pharmacodynamics

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Introduction

Initially introduced for procedural sedation [1], remimazolam has since been approved for general anesthesia in several regions, including South Korea [2]. Recommendations from Korean regulatory authorities—based on a Phase IIb/III investigation conducted in Japan [3]—suggest an induction infusion of 6–12 mg/kg/h [2]. Numerous clinical reports show that remimazolam tends to cause fewer hemodynamic disturbances than propofol and is linked to lower hypotension rates [4–8]. Because individuals of advanced age are particularly susceptible to blood pressure instability during induction [9], these characteristics make remimazolam an appealing option. Findings from other studies indicate that postoperative delirium and recovery profiles are comparable between the two anesthetics [10–12], supporting a likely increase in remimazolam use among older surgical patients. Considerable PK and pharmacodynamic variability in elderly populations, however [13], can result in wide differences in blood pressure responses. A quantitative model describing how remimazolam dose influences BP reductions would therefore be useful for improving anesthetic management.

TCI—an infusion approach that automatically adjusts dosing to maintain a chosen plasma or effect-site concentration based on PK models [14]—typically produces steadier hemodynamics than a fixed continuous infusion [15]. For this reason, many countries routinely apply TCI to propofol administration, although the United States remains an exception [16]. PK models for remimazolam exist [17, 18], but the drug is not yet supported by commercial TCI devices, limiting routine implementation. The current work aimed to build a pharmacodynamic model describing remimazolam-induced BP reduction in patients aged ≥ 65 years, and to indirectly evaluate the potential advantages of TCI by comparing BP changes during induction with commonly used infusion approaches for remimazolam and propofol.

Materials and Methods

Study design

We performed a retrospective assessment of blood pressure measurements, dosing records, and demographic characteristics obtained from a previously completed randomized clinical trial [12]. That study compared postoperative delirium and recovery outcomes in individuals ≥ 65 years undergoing elective gastrectomy with either remimazolam or propofol [12].

Ethical considerations

The original trial received approval from the IRB of Asan Medical Center (Seoul, Korea; 2021–1668, approved November 25, 2021) and adhered to the Declaration of Helsinki. The trial was registered before enrollment began (KCT0006877, December 27, 2021). All participants provided written informed consent permitting academic use of anonymized information.

Patient population

Data from 432 enrolled participants who completed the trial were used. Criteria for enrollment and the randomization process are described in the source publication [12].

Study Procedure

After entering the operating room, patients were connected to standard perioperative monitors, including ECG, pulse oximetry, end-tidal CO_2, and a train-of-four (TOF) device (Carescape B850; GE Healthcare, Milwaukee, Wisconsin, USA). A BIS™ sensor (Medtronic, Dublin, Ireland) was placed on the forehead. All monitor outputs were continuously logged on a computer synchronized to Korean Standard Time. For participants who allowed EEG collection, an eight-channel array was positioned before any anesthetic was given, and at least 5 minutes of baseline EEG was recorded [19]. Patients were kept lying supine for a minimum of 10 minutes to ensure physiologic stability prior to induction. Blood pressure measurements were then obtained every 1 minute after the anesthetic was started.

Loss of consciousness was identified when the participant no longer obeyed the verbal cue “open your eyes.” Rocuronium (0.6 mg/kg) was supplied once unconsciousness was confirmed. Remifentanil administration was then initiated through effect-site TCI based on the Minto model [20], beginning at 2 ng/mL; if systolic pressure remained above 90 mmHg, the target effect-site level was increased to 3 ng/mL. Intubation was performed when both a TOF count of zero and a BIS under 60 were present. To maintain systolic pressure ≥ 80 mmHg and heart rate ≥ 45 bpm, phenylephrine or ephedrine was administered whenever necessary. Blood pressure devices used in the study were recalibrated on a 6-month cycle according to hospital protocol.

Administration of anesthetic agents

Induction dosing for both anesthetic regimens followed routine clinical practice, and no changes were made until the airway was secured. Remimazolam was infused at a constant 6 mg/kg/h. Propofol delivery relied on TCI guided by the Schnider pharmacokinetic model [21, 22], using a target effect-site concentration of 3.5 μg/mL. Infusions were administered via a commercial TCI pump (Perfusor Space; B. Braun Melsungen AG, Germany). To ensure precise dose-timing records, infusion profiles were mirrored in real time using the AsanPump software (version 2.1.5; Bionet Co. Ltd., Seoul, Korea), which was kept synchronized to Korean Standard Time. Any adjustments made at the pump were manually updated in the software. This dual-recording setup allowed exact matching of infusion history with blood pressure data, even though they were logged on different computers.

Development of a Prediction Model

For modeling purposes, blood pressure values were expressed as proportional changes instead of raw measurements. The MBP immediately before induction was assigned a value of 100%, and all subsequent readings were represented as percentage differences from that baseline. Only measurements taken up to the time just before intubation were used. For example, an MBP reduction from 80 mmHg to 64 mmHg corresponded to 80% (64/80). Because intraoperative blood pressure management focuses mainly on MBP rather than systolic pressure [23, 24], modeling was restricted to fractional MBP.

A model that most accurately characterized these fractional values was selected, and a modified logistic function was used [25]. The form of the model is shown in Eq. 1:

$$\text{Fractional MBP} = 100 - \frac{\phi_1}{1 + \exp\left(\frac{\phi_2 - \text{amount}}{\phi_3}\right)} \quad (1)$$

In this framework, ϕ_1 describes the maximum possible decline in fractional MBP as cumulative remimazolam exposure ("amount") becomes very large. ϕ_2 identifies the cumulative dose at which the decrease reaches $\phi_1/2$, representing the midpoint of the curve. ϕ_3 governs how sharply the response shifts around the inflection region. "Amount" refers to the total remimazolam delivered during induction.

Between-subject variability was incorporated using an additive random-effects formulation (Eq. 2):

$$\phi_{ki} = \phi_k + \eta_{ki}, \qquad k = 1, 2, 3 \quad (2)$$

ϕ_{ki} represents the value for individual i; ϕ_k is the typical value; and η_{ki} is a random deviation with mean zero and variance w_k^2. Residual noise within individuals was represented through an additive error model. Model selection relied on the Akaike Information Criterion (AIC) [26]. The following covariates were explored: age, sex, weight, hypertension, and diabetes. Model fitting was performed through the NLMIXED procedure in SAS (version 9.4; SAS Institute Inc., Cary, NC, USA). Simulations using the final parameter estimates were then generated to illustrate covariate-related patterns.

Statistical analysis

The chief objective of this work was to generate a pharmacodynamic framework capable of characterizing how remimazolam influences blood pressure in a dose-responsive manner in adults aged ≥ 65 years. A secondary aim was to provide an indirect comparison of hemodynamic consistency during induction by examining the extent of blood pressure fall in patients given remimazolam via a zero-order infusion versus those receiving propofol through an effect-site targeted approach. Because the primary outcome centered on exploratory model derivation, no formal power assessment was deemed necessary. In contrast, the comparison for the secondary outcome—blood pressure reduction prior to endotracheal intubation—did require a sample size determination. Before the main trial on delirium and recovery metrics was undertaken, a preliminary pilot evaluation was conducted [19]. In that pilot, the percentage decrease in blood pressure from drug initiation to the moment immediately preceding intubation averaged 26.8 ± 9.6% for remimazolam and 24.9 ± 13.4% for propofol. Using a non-inferiority boundary of 5% for the mean between-group difference, along with $\alpha = 0.05$, $\beta = 0.8$, and a projected 5% dropout, the estimated enrollment requirement was 172 participants in each arm.

Statistical procedures were executed with SigmaStat 3.5 (Systat Software, Inc., Chicago, IL, USA), R 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria), and SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Continuous variables were described as mean (standard deviation) when normally distributed and as median (interquartile range) otherwise. Categorical outcomes were reported as n (%). Depending on distribution and variable type, comparisons between groups relied on the two-sample t-test, Mann–Whitney U-test, or the chi-square test.

Results and Discussion

Figure 1 displays the CONSORT diagram. Subjects without complete blood pressure profiles, without matching anesthetic dose records, or with discordant time annotations were excluded. Ultimately, 209 individuals per arm entered the final dataset. Baseline demographic information is provided in **Table 1**, with no meaningful

differences between groups. Parameters related to anesthetic induction, including time to intubation, can be found in **Table 2**. Variability in cumulative doses prior to intubation reflected differences in intrinsic drug potency. **Figure 2** illustrates the trajectory of fractional MBP change from infusion onset to the pre-intubation point, demonstrating progressive MBP decline with increasing cumulative dose in both cohorts. Individualized relative MBP values—defined as the ratio of MBP just before intubation to baseline MBP—are shown in **Figure 3**. Although the reduction in MBP reached statistical significance in favor of a greater decline with remimazolam (72.0 ± 9.9%) compared with propofol (74.2 ± 10.1%; P = 0.024, Student's t-test), the magnitude of this difference was not interpreted as clinically important.

The modified logistic framework effectively captured the dose-response relationship for fractional MBP. In the initial model specification, the scale parameter ϕ_{3i} was fixed. Incorporating body weight as a covariate for both ϕ_{1i} and ϕ_{2i} produced a notable drop in AIC from 7412 (base) to 7369 (covariate model). Other variables, including age and sex, did not exhibit significant associations. Final parameter estimates with standard errors are shown in **Table 3**. For numerical stability, body weight was transformed using weightc = (weight − 40)/60, resulting in values approximately within the 0–1 range. Simulated outcomes displaying the association between cumulative remimazolam dose and fractional MBP, stratified by weight category, are presented in **Figure 4**. Lower body mass resulted in more substantial reductions in MBP at equivalent cumulative doses.

Table 1. Baseline Characteristics

Characteristic	Remimazolam group (n = 209)	Propofol group (n = 209)	P value
Age (years), median (IQR)	74.0 (70.0–78.0)	73.0 (68.0–78.0)	0.196
Female sex, n (%)	74 (35.4%)	66 (31.6%)	0.468
Height (cm), median (IQR)	161.9 (155.4–167.0)	162.6 (155.4–169.0)	0.270
Weight (kg), mean ± SD	62.9 ± 10.1	64.2 ± 10.3	0.219
Body mass index (kg/m²), mean ± SD	24.1 ± 3.2	24.4 ± 3.0	0.440
Comorbidities, n (%)			
Diabetes mellitus	67 (32.1%)	49 (23.4%)	0.063
Hypertension	117 (56.0%)	123 (58.9%)	0.621
ASA physical status, n (%)			0.359
I	2 (0.9%)	2 (0.9%)	
II	194 (92.8%)	186 (89.0%)	
III	13 (6.2%)	21 (10.0%)	
Social history, n (%)			
Current or former alcohol consumption	80 (38.3%)	77 (36.8%)	0.840
Current or former smoking	26 (12.4%)	35 (16.7%)	0.268

Notes: Values expressed as mean (SD), median (25%–75%), or n (%).
ASA PS = American Society of Anesthesiologists physical status.

Table 2. Variables During Anesthetic Induction

Parameter	Remimazolam group (n = 209)	Propofol group (n = 209)	P value	Difference or Relative Risk (95% CI)
Time from initiation of anesthetic to endotracheal intubation (min), median (IQR)	6.2 (5.8–6.6)	6.2 (5.6–8.3)	0.393	–0.4 (–6.3 to 3.0)
Total dose administered until endotracheal intubation (mg), median (IQR)	35.4 (30.6–40.6)	96.1 (83.1–116.6)	< 0.001	–61.4 (–123.7 to –28.1)
Patients requiring ≥1 dose of ephedrine, n (%)	0 (0.0)	2 (1.0)	0.499	–
Patients requiring ≥1 dose of phenylephrine, n (%)	1 (0.5)	0 (0.0)	1.0	–

Patients with mean arterial pressure < 60 mmHg at any time, n (%)	12 (5.7)	13 (6.2)	1.0	Relative risk: 0.923 (0.431–1.975)

Notes: Data reported as mean (SD), median (25%–75%), or n (%). A 5 mg ephedrine bolus was administered to each patient who required it; one participant received 100 μg phenylephrine. Fisher's exact test was used for categorical comparisons. Hodges–Lehmann estimates with 95% confidence intervals were used for continuous variables; categorical data were summarized using relative risks with 95% confidence intervals. Confidence intervals were unobtainable for outcomes with zero events.
CI = confidence interval; MBP = mean blood pressure.

Table 3. Pharmacodynamic Parameter Estimates and Relative Standard Error (RSE) for the Final Model

Parameter	Description	Estimate (SE)	RSE (%)	95% Confidence Interval
$\phi_1 = \phi_{10} + \phi_{11} \cdot \mathrm{WTc}$				
ϕ_{10}	Intercept for maximum MBP reduction (%)	41.23 (2.63)	6.38	36.04 – 46.42
ϕ_{11}	Slope on centered body weight	–20.03 (5.62)	28.06*	–31.11 to –8.94
$\phi_2 = \phi_{20} + \phi_{21} \cdot \mathrm{WTc}$				
ϕ_{20}	Intercept for ED_{50} (mg)	18.60 (1.38)	7.42	15.88 – 21.32
ϕ_{21}	Slope on centered body weight	14.55 (3.34)	22.96	7.96 – 21.13
ϕ_3	Hill coefficient (γ)	5.92 (0.25)	4.22	5.42 – 6.42
Maximum possible reduction	E_{max} (%)	102.08 (14.93)	14.63	72.64 – 131.53
Residual variability	Additive error on fractional MBP change (%)	31.85 (5.41)	16.96	21.19 – 42.51
–	(Multiplicative component not estimated)	–	–	–

Notes: The terms : w_1^2,w_2^2, and w_2^3 denote the variances associated with the interindividual random effects for parameters ϕ _1, ϕ _2, and ϕ _3, respectively. The symbol σ2 corresponds to the variance of the residual component representing within-subject noise. Variability for ϕ _3 was constrained to zero and therefore excluded from estimation.

Body weight was normalized using the expression WTc = (weight − 40)/60. The final pharmacodynamic model used the following structural formulation:

$$\text{Fractional MBP} = 100 - \frac{\phi_{10} + \phi_{11}\mathrm{WTc}}{1 + \exp\left(\frac{(\phi_{20} + \phi_{21}\mathrm{WTc}) - \text{amount}}{\phi_3}\right)} \quad (3)$$

Abbreviations: SE, standard error; RSE, SE/estimate × 100 (%); ϕ_1 upper–lower asymptotic range; ϕ_2, inflection coordinate; ϕ_3, factor governing curve slope.

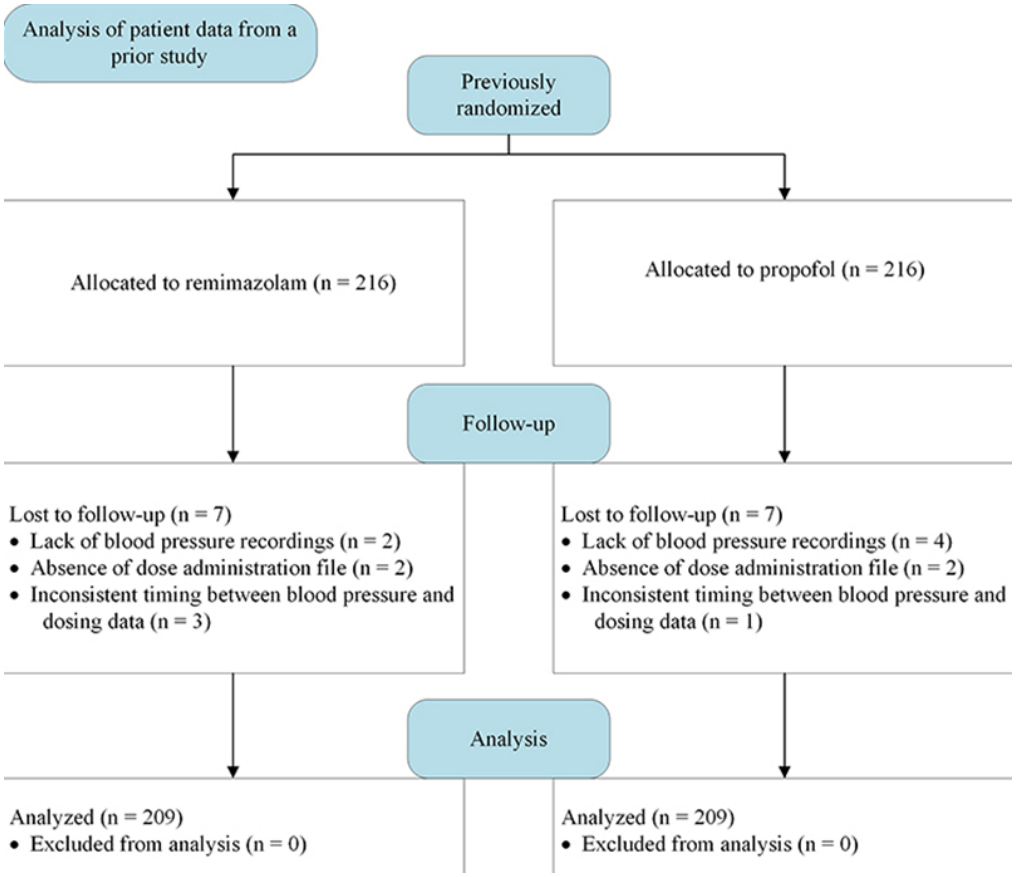
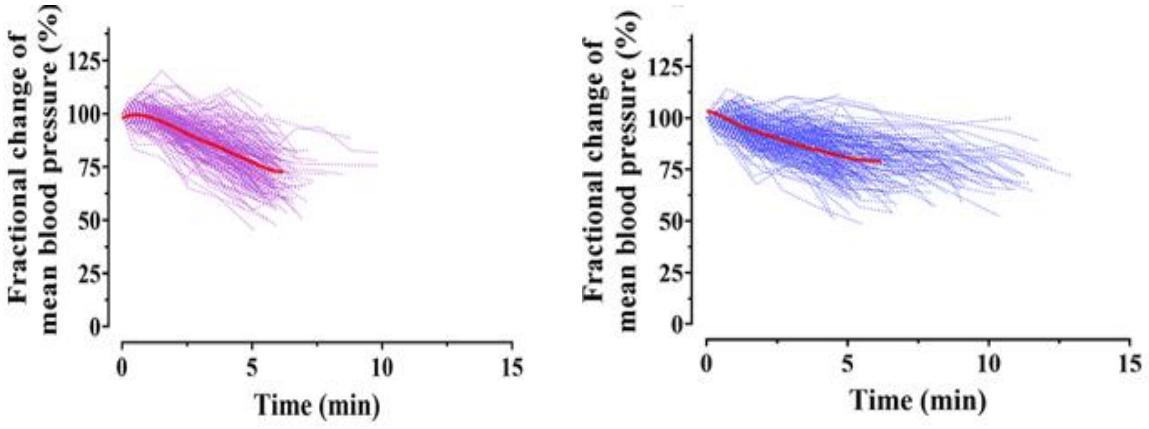


Figure 1. CONSORT diagram. Because the dataset originated from an already completed randomized trial, all enrolled participants passed screening, and none were excluded at that phase.



a) b)

Figure 2. Fractional mean blood pressure (MBP) trajectories following induction with remimazolam (a) and propofol (b). Each dotted trace represents an individual patient's percent MBP change over time. The red continuous curve shows a LOWESS-smoothed trend, drawn up to the average intubation time for the corresponding anesthetic. Fractional MBP was derived by setting the pre-induction MBP to 100%.

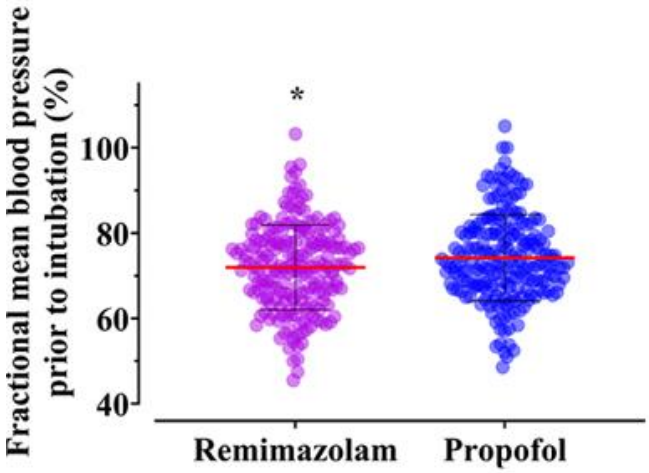
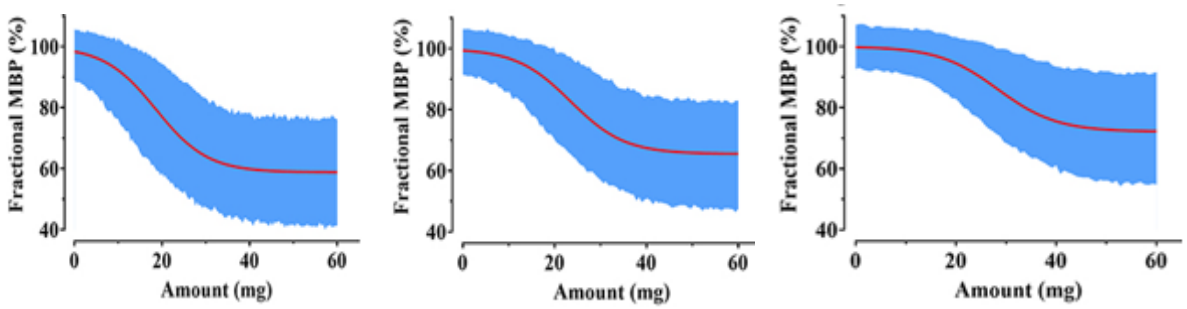


Figure 3. Distribution of fractional MBP immediately prior to endotracheal intubation for the remimazolam and propofol cohorts. Each point corresponds to one subject. Group means appear as red horizontal lines; black vertical bars indicate standard deviations. Fractional MBP was calculated by expressing pre-intubation MBP relative to the 100% baseline. *P < 0.05 versus propofol.



a) b) c)

Figure 4. Stochastic simulations showing how cumulative remimazolam exposure relates to fractional MBP across different body weights. Panels (a), (b), and (c) correspond to simulated patients weighing 40 kg, 60 kg, and 80 kg. Remimazolam infusion was modeled at 6 mg/kg/h using the finalized parameter set. For each weight category, 1,000 Monte-Carlo replicates were generated. The central 50% prediction line appears in red, and the 90% prediction interval is shown in blue shading.

Among individuals aged 65 years and older, reductions in MBP caused by remimazolam during induction were well characterized using a modified logistic formulation, with body weight emerging as a meaningful explanatory covariate. The comparison also suggests that an effect-site–targeted method of anesthetic delivery may confer more stable hemodynamics than constant-rate infusion.

The logistic structure was advantageous for describing the characteristic dose–response pattern of remimazolam, as it accommodates a threshold, a rapid transition region, and a plateau—features that simpler linear or exponential models cannot represent adequately. The model's parameters, including the asymptotic range, the midpoint of the curve, and the slope factor, offer clinically interpretable summaries of these dynamics. The integration of random effects allowed the model to incorporate patient-level variation, improving overall predictive behavior. Considering that remimazolam was infused using a weight-based rate (6 mg/kg/h), identifying weight as a covariate was expected: because infusion rate is tied to mass, and cumulative dose accumulation inherently differs across patients.

TCI remains one of the most sophisticated drug-delivery systems available [16]. Unlike fixed-rate or manually adjusted infusions, TCI algorithms update the infusion rate every ~10 seconds using pharmacokinetic models to maintain a specified target concentration [14]. This enables more accurate titration. When covariates such as weight or age are embedded in the model, intersubject pharmacokinetic variability is partially compensated for, meaning that—even with identical target concentrations and durations—the actual administered dose becomes individualized. Because many anesthetic agents exhibit steep concentration–effect relationships, where small

dosage changes may elicit large physiological responses [27], precise titration is particularly important. TCI therefore offers a meaningful clinical advantage. Its utility has also been explored outside anesthesiology, including for certain antimicrobial therapies [28–30], particularly when maintaining drug concentrations above the minimum inhibitory threshold is crucial.

In patients receiving sedation for endoscopic procedures, propofol delivered through a TCI system has been linked to quicker recovery and fewer episodes of moderate hypotension compared with manually adjusted infusion [31]. These observations support the idea that TCI can help stabilize cardiovascular responses. A previous investigation comparing remimazolam administered at a constant rate with propofol given via effect-site–targeted TCI found no meaningful difference in the extent of MBP decline between the two anesthetics [32]. Although the sample size was small (n = 20 in each arm), limiting the strength of statistical conclusions, the finding that TCI-driven propofol produced hemodynamic effects close to those of remimazolam aligns well with the present results. If remimazolam eventually becomes compatible with TCI platforms, induction may be achieved with even more consistent blood pressure control.

This study has several constraints. First, the dataset available for model development was relatively modest. Predictive models generally benefit from larger, heterogeneous populations, which enhance generalizability and parameter stability [33, 34]. Accordingly, many modeling efforts rely on extensive retrospective databases from routine care [34, 35]. However, cumulative dose information for remimazolam during induction is not automatically captured in usual practice and must be recorded prospectively, naturally restricting the feasible sample size. Despite this, because the central aim here was to construct a pharmacodynamic framework describing the dose–response pattern rather than a clinical prediction tool, the available number of participants was deemed adequate.

Second, comparing hemodynamic responses between two anesthetics that rely on different delivery approaches raises the possibility that the dosing method itself contributes to the observed differences. Ideally, both drugs would be administered using the same strategy to rule out such confounding. Nonetheless, using an approach not routinely applied in actual clinical practice would reduce the relevance of the results. In Korea, remimazolam is not yet integrated into approved TCI pumps, whereas propofol TCI is standard. For this reason, the study retained the typical real-world administration protocol for each agent rather than enforcing uniformity solely for experimental symmetry. Notably, the fact that propofol infused using effect-site TCI produced a blood pressure decrease comparable to that of constant-rate remimazolam suggests that TCI may be advantageous for modulating hemodynamic changes during induction.

Third, plasma concentrations of remimazolam were not obtained, preventing a direct assessment of concentration–effect dynamics. Without such measurements, interpretations may be influenced by the titration paradox. Collecting concentration data would enable explicit analysis of pharmacokinetic–pharmacodynamic coupling. However, because the parent trial focused on postoperative delirium rather than PK sampling, intraoperative blood draws were not performed. Even so, the incorporation of interindividual variability into the pharmacodynamic model helps preserve analytical reliability.

Conclusion

Among older adults (≥65 years) undergoing general anesthesia with remimazolam, the association between drug exposure and MBP reduction during induction was effectively described using a modified logistic function, with body weight serving as a notable modifier. Although remimazolam delivered at a fixed infusion rate produced a statistically larger MBP decrease than propofol administered with TCI, the magnitude of this difference did not reach clinical relevance.

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Ethics Statement: None

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