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Remimazolam Enables Faster Sedation Induction and Recovery Compared With Midazolam in Diagnostic Upper Gastrointestinal Endoscopy: A Multicenter Randomized Controlled Trial

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ABSTRACT

Background and Aims: Remimazolam, a new ultra-short-acting benzodiazepine, is a safe and effective option for procedural sedation. Nevertheless, to date, no study has directly compared remimazolam and midazolam in diagnostic upper gastrointestinal endoscopy. This study aimed to evaluate the efficacy and safety of remimazolam compared with those of midazolam in this setting.

Methods: This multicenter, single-blind, randomized, positive-control, superiority, investigator-initiated phase III trial enrolled patients who were scheduled to undergo diagnostic upper gastrointestinal endoscopy at seven academic teaching hospitals from April 2023 to January 2024. Participants were randomly assigned to receive remimazolam or midazolam (1:1 ratio). The primary endpoint was total procedure time, defined as the duration from the first sedative administration to discharge.

Results: Of 133 randomized patients, 132 (remimazolam group, $n = 66$; midazolam group, $n = 66$) underwent upper endoscopy with sedation. The total procedure time was significantly shorter in the remimazolam group (30.3 vs. 48.5 min, $p < 0.001$). Sedation-related times (i.e., induction, sedation, recovery, and discharge times) were also significantly shorter in the remimazolam group (all $p < 0.001$). The incidence of adverse events did not significantly differ between the groups; however, the incidence rates of hypotension, bradycardia, and paradoxical reactions were lower in the remimazolam group. When compared to previous sedation experiences, patient satisfaction was higher in the remimazolam group ($p < 0.001$).

Conclusions: Compared with midazolam, the use of remimazolam in diagnostic upper gastrointestinal endoscopy allows for faster sedation induction and recovery, more rapid discharge, and higher patient satisfaction compared with previous sedation experiences, while maintaining a safety profile similar to that of midazolam.

Trial registration: ClinicalTrials.gov (NCT05836545)

Jun Kyu Lee deceased October 6, 2025.

Presentation: Preliminary data for this study were presented as an oral presentation at the ESGE (European Society of Gastrointestinal Endoscopy) days, 3–5 April 2025, Barcelona.

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Key Summary

- Summarise the established knowledge on this subject
  - Remimazolam, a new ultra-short-acting benzodiazepine, is a safe and effective option for procedural sedation.
  - No study has yet directly compared remimazolam and midazolam in diagnostic upper gastrointestinal endoscopy.
- What are the significant and/or new findings of this study?
  - Remimazolam significantly reduced total procedure time compared with midazolam in diagnostic upper gastrointestinal endoscopy.
  - Remimazolam enabled faster sedation induction and quicker recovery while maintaining a safety profile comparable to midazolam.
  - Compared to previous sedation experiences, a significantly higher proportion of patients in the remimazolam group reported greater satisfaction.

1 | Introduction

Gastrointestinal endoscopic sedation is widely performed to reduce patients' anxiety and discomfort and to facilitate thorough examinations [1, 2]. Although gastrointestinal endoscopic sedation is generally considered safe, the administration of sedative drugs may lead to adverse events, underscoring the ongoing clinical need for effective and safer agents.

Midazolam and propofol are widely utilized worldwide as primary agents for sedation during endoscopic procedures [3–5]. Midazolam, a short-acting benzodiazepine, is favored over propofol because it is associated with relatively fewer episodes of cardiorespiratory depression; nevertheless, its slower onset of 2–3 min, longer half-life (1.8–6.4 h), and cumulative effects from active metabolites result in prolonged sedation and less predictable recovery time [6–8]. Propofol is valued for its rapid onset and offset, potent sedative effect, and high patient satisfaction; however, propofol is associated with risks of cardiovascular and respiratory depression without an available antagonist [9, 10].

Remimazolam is a new ultra-short-acting benzodiazepine, which integrates the carboxylic ester moiety to enhance GABA-A receptor activity and is rapidly hydrolyzed into inactive metabolites by nonspecific tissue esterases, thereby merging the safety of midazolam with the rapid onset, fast recovery, and sufficient sedative effect of propofol [11]. This profile has positioned remimazolam as a safe and effective option for procedural sedation, as evidenced by multiple clinical studies [12–17]. The rapid sedation, fast recovery, and effective sedative properties of remimazolam offer particular advantages over midazolam in diagnostic upper gastrointestinal endoscopy, which generally requires shorter procedure times. Nevertheless, to date, no study has directly compared remimazolam and midazolam in this context. Therefore, the present randomized controlled trial aimed to evaluate the efficacy and safety of remimazolam compared with those of midazolam in diagnostic upper gastrointestinal endoscopy.

2 | Methods

2.1 | Study Design

This multicenter, prospective, randomized, single-blind, positive-control, parallel, clinical trial was designed as a superiority trial evaluating and analyzing the efficacy and safety of remimazolam compared with those of midazolam in diagnostic upper gastrointestinal endoscopy. Patients were recruited from seven academic teaching hospitals across South Korea from April 2023 to January 2024 and were randomized to receive either remimazolam or midazolam at a 1:1 ratio (Supporting Information S1: Figure S1).

This study was approved by the Institutional Ethics Review Board of Samsung Medical Center, Sungkyunkwan University School of Medicine on September 23, 2022 (IRB approval no. 2022-08-031, Hojoong Kim) and the IRBs of participating institutions including Dongguk University Ilsan Hospital, Ewha Womans University Seoul Hospital, Yeungnam University Hospital, Chosun University Hospital, Seoul National University Boramae Medical Center, and Chungnam National University Hospital. The trial adhered to the Declaration of Helsinki principles and was registered at ClinicalTrials.gov (NCT05836545). All participants provided voluntary written informed consent after receiving detailed study information and discussing any questions with investigators. The confidentiality of participant identities was strictly maintained.

2.2 | Inclusion and Exclusion Criteria

The participants were screened for eligibility within 4 weeks prior to randomization during the screening period, when informed consent was obtained. The eligibility criteria for enrollment were as follows: (i) being scheduled for diagnostic upper gastrointestinal endoscopy under sedation, with an expected endoscopic procedure time of 15 min or less; (ii) age of 19–60 years; (iii) American Society of Anesthesiologists (ASA) score of 1 or 2 [1]; (iv) body mass index (BMI) $\geq$ 18.5 kg/m^2 and $<$ 30 kg/m^2; and (v) capability of understanding the study's purpose, methods, and effects and voluntarily signing a written consent form after receiving an explanation.

The exclusion criteria for this trial were as follows: (i) suspected pathological conditions in the gastrointestinal tract that may require therapeutic endoscopy; (ii) a history of respiratory diseases that could affect adequate breathing during sedation, such as chronic obstructive pulmonary disease, respiratory disorders from cerebrovascular or musculoskeletal disorders, or those with tracheal cannulas; (iii) Mallampati score $\geq$ 3 [1], indicating difficulty in maintaining an airway, or sleep apnea syndrome; (iv) pre-randomization systolic blood pressure (SBP) $>$ 160 mmHg or $<$ 90 mmHg; (v) uncontrolled hypertension; (vi) acute narrow-angle glaucoma; (vii) severe hepatic dysfunction or chronic kidney disease; (viii) a history of drug or alcohol abuse

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within the past year; (ix) hypersensitivity to benzodiazepines, remimazolam components (e.g., dextran), or any components of midazolam; (x) genetic conditions such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption; (xi) pregnancy, breastfeeding, or a positive pregnancy test result at screening; (xii) participation in other clinical trials within 1 month prior to screening; (xiii) inability to provide informed consent; and (xiv) any condition that could render a participant unsuitable for the trial, as judged by the principal investigator.

2.3 | Randomization

Within 15 min from the start of the endoscopic procedure, eligible participants were randomized in a 1:1 ratio to receive either remimazolam or midazolam. The random allocation method, prepared pre-trial, included the following steps: (i) generating random allocation codes using SAS software version 9.4 (SAS Institute Inc., USA), and (ii) assigning participants to groups according to these codes provided for each institution. At trial sites, investigators confirmed participant eligibility based on inclusion and exclusion criteria. Each eligible participant received a unique allocation number for prescribing and administering the trial medication. Blinding was maintained for participants after randomization (single-blind).

2.4 | Sedation and Endoscopy Procedures

After randomization, patients received an initial dose of either 5 mg remimazolam or 2 mg midazolam, each administered over > 1 min using a syringe through an intravenous push before the start of the procedure. The consciousness level was assessed using the Modified Observer's Assessment of Alertness and Sedation (MOAA/S) score. The procedure was commenced once adequate sedation (defined as MOAA/S score ≤ 3) was achieved. If adequate sedation was not achieved with the initial dose, or if the depth of sedation decreased during the procedure, additional doses of 2.5 mg of remimazolam or 1–2 mg of midazolam were administered at a minimum interval of 2 minutes, up to a maximum of five times within 15 min. The consciousness level was assessed before sedative administration at the start of the procedure, and subsequently at 1, 1.5, 2, 2.5, 3, 4, and 5 min after sedative administration, continuing every 2 minutes until full recovery of consciousness (defined as a MOAA/S score of 5 on three consecutive assessments) was achieved. If adequate sedation was not achieved after the initial dose and up to five additional doses, rescue medication such as propofol was administered at the investigators' discretion; this was designated as sedation failure. Flumazenil was used if consciousness did not return at > 30 min after the last sedative dose, starting with 0.2 mg and adding 0.1 mg every minute up to a total maximum dose of 1 mg if necessary.

Heart rate and oxygen saturation were continuously monitored from sedative administration until full recovery of consciousness with supplemental oxygen being provided as necessary. Vital signs, including SBP, diastolic blood pressure (DBP), pulse rate, respiratory rate, and oxygen saturation, were measured prior to sedative administration, at the start of the endoscopic procedure, 3 minutes after sedative administration, and then every 5 minutes until discharge. Adverse events were monitored every 5 minutes until discharge.

Upon the full recovery of consciousness, participants were discharged from the recovery room when their Aldrete score exceeded 9. Patient satisfaction was assessed at discharge using a self-reported questionnaire with four items: overall satisfaction, comfort level, willingness to recommend the sedative to others, and comparison to previous endoscopic procedures (Supporting Information S1: Figure S2).

An independent research nurse, not involved in the endoscopic or sedation administration team, accompanied each patient from the initial sedative injection through to discharge. Standardized time-points (sedative administration, scope insertion, withdrawal, last sedative dose, and discharge) were recorded using a stopwatch and predefined case report form, in order to ensure consistency and minimize measurement bias.

2.5 | Clinical Outcome Measurements

The primary endpoint was the total procedure time defined as the duration from the first sedative administration to discharge. This includes the sedative induction, the actual endoscopic procedure (insertion-to-retrieval), recovery, and discharge phases. Because the procedure was limited to diagnostic upper gastrointestinal endoscopy—a setting in which the actual endoscopic insertion-to-retrieval time (total endoscopy time) is typically brief and shows minimal inter-individual variability—the total procedure time was considered a meaningful composite measure of sedative performance, encompassing induction, procedural, recovery, and discharge components. The secondary endpoints were the sedation success rate, recovery time, induction time, total endoscopy time, discharge time, sedation time, patient satisfaction (4-item self-reported questionnaires), and incidence rates of hypotension (SBP ≤ 80 mmHg, DBP ≤ 40 mmHg, or ≥ 20% decrease in SBP or DBP from baseline), respiratory depression (oxygen saturation < 90% for > 1 min), tachycardia (heart rate > 100/min or ≥ 20% increase from baseline), bradycardia (heart rate < 60/min or ≥ 20% decrease from baseline), and paradoxical reaction. The sedation success rate was defined as the completion of the endoscopy procedure with up to five supplemental doses within 15 min after the initial dose and no requirement for a rescue sedative. Sedation time and recovery time were defined as the duration from initial and last sedative administrations, respectively, to the full recovery of consciousness, which is measured as the first assessment point at which the MOAA/S score reached 5 for three consecutive times. Induction time was defined as the time from the first sedative administration to adequate sedation (MOAA/S score ≤ 3). Total endoscopy time covered from endoscope insertion to endoscope retrieval, and discharge time from endoscope retrieval to discharge. The primary and secondary outcomes are summarized in Supporting Information S1: Figure S3.

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2.6 | Statistical Analysis

The sample size for this superiority trial was based on a previous study where the mean total procedure time for midazolam in upper endoscopy was 48.3 min [18]. Remimazolam was expected to reduce this by 15% (7.245 min), setting an effect size of 7.245 min. Lacking a reported standard deviation (SD) from the previous study, we assumed a normally distributed total procedure time, conservatively setting the SD at 12.075 (calculated as the SD for which 48.3–4 SD = 0) and assuming it to be identical across both groups. With a one-sided 2.5% significance level and 90% power for primary hypothesis testing using the two-sample *t*-test, the required sample size was calculated as 120 participants (60 per group) using PASS software version 22.0.2. This was adjusted to 132 participants (66 per group) to account for a 10% dropout rate (Supporting Information S1: Figure S4).

Efficacy analysis used an intention-to-treat (ITT) approach, including all randomized participants who received sedatives, underwent endoscopy, and had at least one post-randomization efficacy assessment, maintaining their original group assignments. Results were evaluated using the full analysis set (FAS), aligning with ITT principles and including patients with any primary efficacy endpoint data. The per-protocol set (PPS) included all randomized patients who completed the study without major protocol deviations. Secondary safety outcomes were analyzed using the safety analysis set (SS) comprising all patients who received sedatives and were analyzed according to the actual medication received.

Statistical analyses were conducted using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as means ± SD or medians with ranges for continuous variables, and frequencies and percentages for categorical variables. The normality of continuous variables was assessed using the Shapiro–Wilk test at a 5% significance level. Differences between groups were analyzed using two-sample t-tests or Wilcoxon rank-sum tests for continuous variables based on the normality, and chi-squared or Fisher's exact tests for categorical variables, depending on expected frequencies.

The superiority of remimazolam over midazolam for the primary efficacy endpoint (total procedure time) was analyzed using a one-sided two-sample *t*-test with a p value < 0.025 indicating superiority. A two-sided 95% confidence interval was also provided for the difference in mean total procedure times between the treatment groups. Secondary endpoints were analyzed similarly, with a two-sided p value of < 0.05 indicating significant difference in incidence rates between the treatment groups.

3 | Results

3.1 | Randomization Results and Baseline Patient Characteristics

In total, 133 eligible participants at seven centers were randomized, including 67 patients treated with remimazolam and 66 patients treated with midazolam. Among them, 132 (remimazolam group, $n = 66$; midazolam group, $n = 66$) received the assigned sedative agents and were included in the FAS and SS. However, one participant in the remimazolam group was later found to have not met the inclusion criteria (BMI ≥ 18.5 kg/m^2), and two participants (one in each group) with Mallampati class 3—contrary to our exclusion criterion of Mallampati ≥ 3—were identified as protocol deviations. These three participants were then excluded from the efficacy analysis. Two participants in the midazolam group were excluded from the per-protocol population because of sedation failure with midazolam and additional use of contraindicated drugs (propofol and pethidine). An overview of the study progress and patient enrollment is presented in Figure 1.

The baseline characteristics of the FAS participants are summarized in Table 1. The median age was 42 and 39 years in the

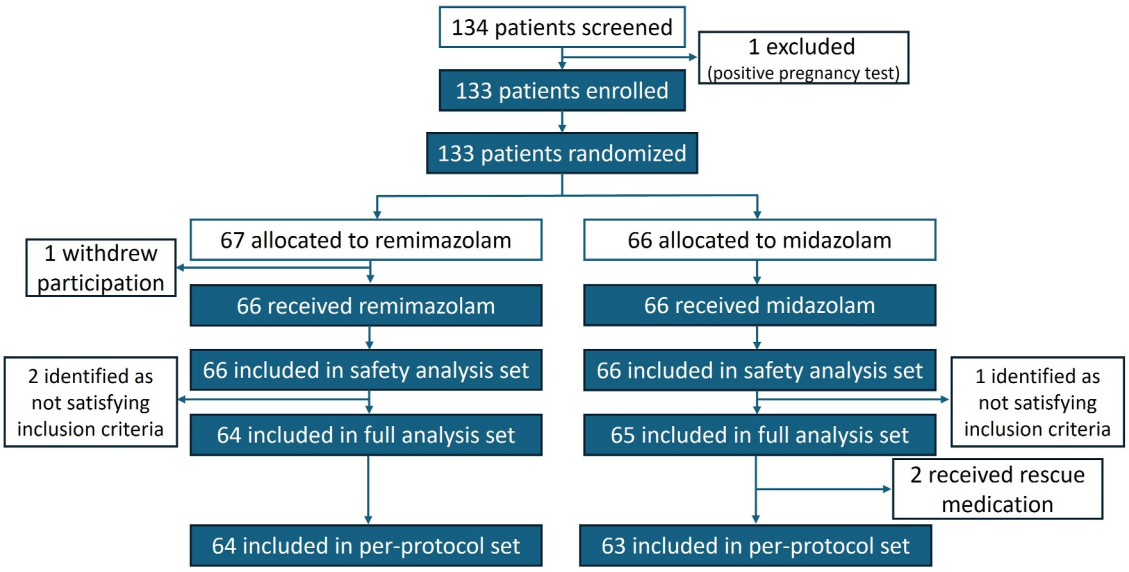


FIGURE 1 | Overview of the study progress and patient enrollment status.

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remimazolam and midazolam groups, respectively. Male patients accounted for 42.2% and 33.8% in the remimazolam and midazolam groups, respectively. No significant differences in demographics and baseline vital signs were observed between the two groups (all $p > 0.05$), except for DBP.

3.2 | Primary Efficacy Outcome

The mean total procedure time was significantly shorter in the remimazolam group than in the midazolam group (30.3 ± 6.8 min vs. 48.5 ± 12.5 min, $p < 0.001$) (Table 2 and Figure 2).

3.3 | Secondary Efficacy Outcomes

The results for the secondary efficacy outcomes in the FAS are presented in Table 3. The overall success rate of sedation was comparable between the remimazolam and midazolam groups (100% vs. 97%, $p = 0.496$), with all participants in both groups completing the endoscopy procedure and receiving up to five supplemental doses within 15 min after the initial dose. However, two participants in the midazolam group failed to achieve adequate sedation even after the administration of five supplemental doses: one required additional propofol, whereas the other required pethidine. None of the participants received flumazenil.

TABLE 1 | Baseline characteristics of the participants in the full analysis set.

Characteristic	Remimazolam ($n = 64$)	Midazolam ($n = 65$)	p value
Age, years, median (IQR)	42.0 (15.5)	39.0 (15.0)	0.417
Male, *n* (%)	27 (42.2%)	22 (33.8%)	0.329
Height, cm, median (IQR)	165.2 (10.00)	164.0 (13.8)	0.490
Weight, kg, median (IQR)	62.9 (21.10)	61.0 (17.8)	0.449
BMI, kg/m^2, median (IQR)	23.1 (4.5)	22.9 (5.2)	0.611
ASA score, *n* (%)			1.000
1	62 (96.9%)	62 (95.4%)	
2	2 (3.1%)	3 (4.6%)	
Mallampati score, *n* (%)			0.800
1	36 (56.3%)	38 (58.5%)	
2	28 (43.7%)	27 (41.5%)	
Current smoker, *n* (%)	10 (15.6%)	7 (10.8%)	0.415
Current alcohol drinker, *n* (%)	33 (51.6%)	43 (66.2%)	0.092
Systolic blood pressure, mmHg, mean (SD)	119.9 (13.5)	124.5 (14.9)	0.096
Diastolic blood pressure, mmHg, mean (SD)	73.3 (10.9)	78.9 (12.0)	0.008
Pulse rate, times/min, median (IQR)	76.0 (22.0)	76.0 (18.0)	0.568
Oxygen saturation, %, median (IQR)	99.0 (2.0)	98.0 (2.0)	0.480
Laboratory result			
AST, IU/L, median (IQR)	20.5 (6.0)	21.0 (7.0)	0.879
ALT, IU/L, median (IQR)	17.5 (13.8)	19.0 (13.0)	0.946
Total bilirubin, mg/dL, median (IQR)	0.6 (0.3)	0.6 (0.4)	0.619
Blood urea nitrogen, mg/dL, median (IQR)	12.3 (6.0)	12.0 (5.1)	0.937
Creatinine, mg/dL, median (IQR)	0.7 (0.3)	0.7 (0.3)	0.709

Abbreviations: ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; BMI, body mass index; IQR, interquartile range; SD, standard deviation.

TABLE 2 | Primary efficacy outcomes in the full analysis set (FAS) and per-protocol set (PPS).

Population		Remimazolam	Midazolam	p value
FAS	Number of patients	64	65	< 0.001
	Total procedure time, min, mean (SD)	30.3 (6.8)	48.5 (12.5)	
PPS	Number of patients	64	63	< 0.001
	Total procedure time, min, mean (SD)	30.3 (6.8)	48.5 (12.6)	

Abbreviations: FAS, full analysis set; PPS, per-protocol set; SD, standard deviation.

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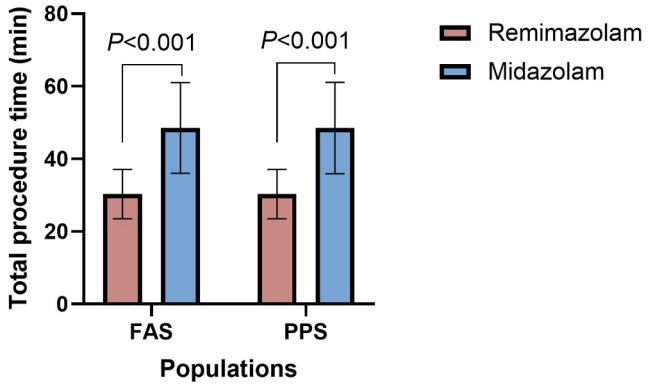


FIGURE 2 | Comparison of total procedure time between the remimazolam and midazolam groups.

TABLE 3 | Secondary efficacy outcomes in the full analysis set.

Outcome	Remimazolam ($n = 64$)	Midazolam ($n = 65$)	p value
Success rate of sedation, n (%)	64 (100%)	63 (97%)	0.496
Recovery time, min, median (range)	13.0 (4.0–31.0)	28.2 (2.0–57.0)	< 0.001
Discharge time, min, mean (SD)	23.5 (7.2)	38.8 (13.0)	< 0.001
Sedation time, min, mean (SD)	16.9 (6.5)	33.7 (12.6)	< 0.001
Induction time, min, median (range)	1.9 (1.0–13.0)	3.0 (1.0–17.0)	< 0.001
Total endoscopy time, min, median (range)	4.0 (1.3–7.0)	4.0 (1.9–10.8)	0.724

Abbreviation: SD, standard deviation.

As for the other secondary efficacy outcomes, the recovery, induction, sedation, and discharge times were significantly shorter in the remimazolam group than in the midazolam group (all $p < 0.001$). The total endoscopy time (i.e., the duration of the actual endoscopic procedure) was similar between the two groups. These results were consistent in the FAS and PPS populations (Supporting Information S1: Table S1).

3.4 | Safety Outcomes

The incidence of adverse events is detailed in Table 4. During screening and baseline examinations, no differences in heart rate, SBP, DBP, and oxygen saturation were identified between the groups. Overall, there were no statistically significant differences in adverse events between the groups. Although not statistically significant, hypotension was less frequent in the remimazolam group than in the midazolam group (33.3% vs. 48.5%). Most hypotensive cases were those in which SBP or DBP decreased by ≥ 20% from baseline; only one case in the midazolam group had an SBP ≤ 80 mmHg. Bradycardia also occurred less frequently in the remimazolam group than in the midazolam group (15.2% vs. 27.3%), with the lowest pulse rate showing a significant difference (remimazolam group: median, 76.5 [range, 55–103]; midazolam group: median, 66 [range, 51–100]; $p < 0.001$) (Supporting Information S1: Table S2). No cases of respiratory depression were identified in either group. Two cases in the remimazolam group exhibited transient hypoxemia ($SpO_2 < 90\%$) but immediately recovered within 1 min after oxygen administration.

TABLE 4 | Incidence of adverse events in the safety analysis set.

Adverse events, n (%)	Remimazolam ($n = 66$)	Midazolam ($n = 66$)	p value
Hypotension	22 (33.3%)	32 (48.5%)	0.08
Systolic hypotension	11 (16.7%)	19 (28.8%)	0.09
Diastolic hypotension	19 (28.8%)	28 (42.4%)	0.10
Respiratory depression	0	0	—
Cardiac disorders			
Tachycardia	43 (65.2%)	41 (62.1%)	0.72
Bradycardia	10 (15.2%)	18 (27.3%)	0.09
Paradoxical reaction	9 (13.6%)	13 (19.7%)	0.35
Nausea	2 (3.0%)	0	0.50
Headache	0	1 (1.5%)	1.00

3.5 | Patient Satisfaction

Overall, patient satisfaction was similar between the two groups; however, the proportion of patients who felt that their experience was better than their previous sedation experiences was significantly higher in the remimazolam group (56.3% vs. 20.0%, $p < 0.001$) (Supporting Information S1: Table S3).

3.6 | Sedative Dosing

The median total remimazolam dose was 7.5 mg (range, 5.0–17.5 mg) compared to 5.0 mg for midazolam (range, 2.0–12.0 mg). The median number of additional doses was one for remimazolam and two for midazolam, with the remimazolam group receiving significantly fewer additional administrations ($p < 0.001$). In the remimazolam group, 21.9% were adequately sedated with only the loading dose, and 57.8% completed the upper endoscopy with the loading dose or one additional administration. In contrast, all but one patient in the midazolam group required additional doses, with 86.2% requiring at least two additional doses and 46.2% requiring three or more doses (Supporting Information S1: Table S4 and Figure S5).

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3.7 | Sedation Level

The MOAA/S score over time after the administration of the study medications is shown in Figure 3. The mean MOAA/S score attained at the deepest sedation level was 1.9 ± 0.9 in the remimazolam group, which was significantly lower than the score of 2.3 ± 0.7 in the midazolam group ($p = 0.040$). Furthermore, the mean time to reach the lowest MOAA/S score was significantly shorter in the remimazolam group than in the midazolam group (3.1 ± 2.5 min vs. 6.4 ± 4.8 min, $p < 0.001$) (Supporting Information S1: Table S5).

4 | Discussion

This multicenter, single-blind, randomized, positive-control, superiority, investigator-initiated phase III trial evaluated the efficacy and safety of remimazolam compared with those of midazolam in diagnostic upper gastrointestinal endoscopy. Remimazolam significantly reduced the total procedure time—from a mean of 48.5 to 30.3 min ($p < 0.001$)—despite nearly identical actual endoscopy insertion-to-retrieval times in both groups. This difference therefore reflects a reduction in sedation-related periods, including induction, maintenance and recovery phases. In this study, remimazolam facilitated a more rapid sedation induction (median: 1.9 vs. 3.0 min) and a faster recovery time (13.0 vs. 28.2 min) compared with midazolam (all $p < 0.001$). This efficiency is particularly advantageous for upper gastrointestinal endoscopy, in which the procedure time is generally short, allows for faster turnover in the recovery room, and expedites patient discharge.

Although concerns exist about frequent dosing owing to the ultra-short action of remimazolam [16], over half of the patients in the remimazolam group in this study were adequately sedated with one or no additional doses. In a previous colonoscopy study, an initial dose and an average of 2.2 additional doses of remimazolam were sufficient to sedate an average patient, achieving a procedural success rate of 91.3% [12]. This number of additional doses may be similar to or less than that required for midazolam, depending on the administration rate and dosage of midazolam. In this study, over 20% of the patients were adequately sedated with only a loading dose of remimazolam, whereas all but one individual in the midazolam group required additional doses. Such a streamlining of medication administration can reduce the need for extra staff and alleviate the inconveniences associated with frequent dosing.

Furthermore, remimazolam achieved a deeper level of sedation more quickly (mean MOAA/S score achieved at the deepest sedation level: 1.9 vs. 2.3 within 3.1 vs. 6.4 min) while maintaining a safety profile comparable to that of midazolam. Although this was not directly associated with overall patient satisfaction, significantly more patients in the remimazolam group reported greater satisfaction compared with previous sedation based on propofol or midazolam.

In relation to sedative dosage, other studies have used lower midazolam doses (1.75 mg for those under 60 years of age) than typical sedation practices [12, 13]. However, in this study, the midazolam dose was higher than that in other studies, aligning with the doses typically used for sedation. Nevertheless, remimazolam demonstrated a superior profile in terms of time to adequate sedation, deepest MOAA/S score, sedation success rate, and number of additional doses needed compared with midazolam. Additionally, although remimazolam led to a significantly faster recovery time in this study, midazolam is often used at even higher doses and faster rates, suggesting that the advantages of remimazolam in terms of recovery speed could be even more pronounced in real-world settings.

Regarding the safety profile of remimazolam, studies comparing it with midazolam found no significant differences in adverse events, consistent with this study's findings. However, remimazolam showed fewer instances of hypotension and bradycardia. There were two cases of transient hypoxemia in the remimazolam group, but they immediately resolved with oxygen supply and thus did not meet the definition of respiratory depression (oxygen saturation < 90% for more than 1 min). Therefore, the safety profile of remimazolam is similar to that of midazolam.

Some studies have compared remimazolam with propofol in upper endoscopy, and others have compared remimazolam with midazolam in different procedures such as colonoscopy and bronchoscopy. However, this study has significance in that this is

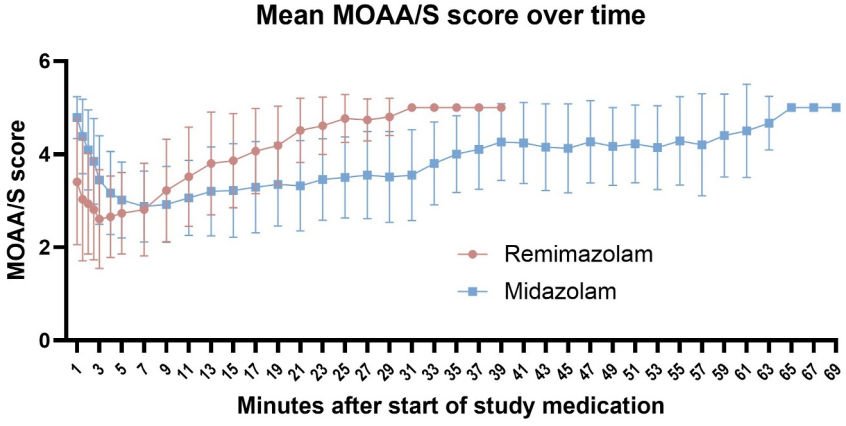


FIGURE 3 | Changes in the modified observer's assessment of alertness and sedation (MOAA/S) scale scores over time after administration of study medications.

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the first randomized controlled trial to compare remimazolam with midazolam, specifically in upper endoscopy. In previous studies comparing remimazolam with propofol in upper endoscopy, remimazolam demonstrated a noninferior sedation success rate to propofol, and it has shown superior safety profiles and recovery times [15, 16]. In this study, remimazolam exhibited faster sedation induction and recovery compared with midazolam while maintaining a similar safety profile. In summary, findings from previous studies along with those from our current study suggest that remimazolam is noninferior to propofol and superior to midazolam in terms of sedative efficacy during upper endoscopy. Regarding safety, remimazolam was superior to propofol and comparable to midazolam, effectively merging the efficacy and safety profiles of both drugs. Additionally, remimazolam appeared to have the fastest recovery time among the three agents. However, further research is required to confirm these findings.

Fentanyl was used in conjunction in studies comparing remimazolam with midazolam for other procedures such as colonoscopy and bronchoscopy, as well as in studies comparing remimazolam with propofol in upper endoscopy. However, in this study, fentanyl was not used, and remimazolam alone was sufficient to achieve rapid and adequate sedation as well as higher patient satisfaction compared to previous sedation experiences with midazolam or propofol.

This study has a few limitations. First, participants were followed up to the point of discharge owing to protocol simplification, suggesting that further research with an extended follow-up period post-discharge could provide additional insights. Second, the study included only ASA 1 and 2 patients undergoing diagnostic endoscopy. Additional studies are required to determine whether remimazolam can similarly deliver more satisfactory sedation efficacy, similar safety, and faster recovery compared to midazolam in patients with ASA three or higher or in procedures requiring longer upper gastrointestinal endoscopy times. Third, although we employed a benzodiazepine-only protocol without opioid supplementation to assess the intrinsic performance of remimazolam compared with midazolam, the absence of opioid co-administration may limit external validity in settings where opioid supplementation is routinely practiced. Moreover, the use of fixed rather than weight-based midazolam dosing may also limit generalizability in clinical environments where weight-based dosing is standard practice. Considering that dosing regimens may vary across jurisdictions, future studies should evaluate these agents under a broader range of dosing regimens and in settings with routine opioid co-administration. Fourth, although the median total endoscopy time (insertion to retrieval) was 4 min in both groups and did not differ significantly, variability in procedure duration can become meaningful in other endoscopic settings—especially therapeutic or more complex interventions. Thus, while our primary endpoint of total procedure time was appropriate for diagnostic upper gastrointestinal endoscopy, its applicability may be limited in contexts where endoscopy itself takes longer or exhibits greater case-to-case variability. Fifth, recruitment was challenging because all participating centers were academic institutions focused on therapeutic endoscopy, and eligibility was restricted to ASA I–II patients undergoing diagnostic upper gastrointestinal endoscopy. Coupled with an exclusion criterion allowing investigator-discretion exclusion of any participant deemed unsuitable, these factors may have introduced selection bias. Sixth, although the study was powered to detect differences in the primary endpoint of total procedure time, the sample size is inadequate for robust comparisons of infrequent adverse events, which may limit the evaluation of safety differences between groups. Finally, patient-reported satisfaction may have been influenced by participation awareness, and the single-blind design may have increased physicians' attentiveness to patient comfort, introducing potential response and observer bias when comparing satisfaction with prior experiences.

In conclusion, this study confirmed that compared with midazolam, the use of remimazolam in diagnostic upper gastrointestinal endoscopy allows for faster sedation induction and recovery, more rapid discharge, and higher patient satisfaction compared with previous sedation experiences, while maintaining a safety profile similar to that of midazolam. Remimazolam is a safe and effective sedative for outpatient upper gastrointestinal endoscopy.

Author Contributions

Conceptualization, K.H.L. and J.K.L. Methodology, J.K.L. and T.K. Software, Y.P. Validation, Y.P., K.H.L. and J.K.L. Formal Analysis, Y.P. Investigation, Y.P., J.K.L., K.H.L., T.K., S.H.K., D.-W.A., S.B.K. and S.J.K. Resources, J.K.L., K.H.L. and Y.P. Data Curation, Y.P., K.H.L. Writing – Original Draft Preparation, Y.P. Writing – Review and Editing, Y.P., J.K.L. and K.H.L. Visualization, Y.P. Supervision, J.K.L. and K.H.L. Project Administration, K.H.L. and J.K.L. Funding Acquisition, K.H.L. and J.K.L. All authors have approved the final version of the article, including the authorship list.

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Ethics Statement

This study was approved by the Institutional Ethics Review Board of Samsung Medical Center, Sungkyunkwan University School of Medicine on September 23, 2022 (IRB approval no. 2022-08-031, Hojoong Kim) and the IRBs of participating institutions including Dongguk University Ilsan Hospital, Ewha Womans University Seoul Hospital, Yeungnam University Hospital, Chosun University Hospital, Seoul National University Boramae Medical Center, and Chungnam National University Hospital. The trial adhered to the Declaration of Helsinki principles.

Consent

All participants provided voluntary written informed consent after receiving detailed study information and discussing any questions with investigators. The confidentiality of participant identities was strictly maintained.

Conflicts of Interest

The authors declare no conflicts of interest.

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The authors have nothing to report.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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