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Original Article

Effect of remimazolam on oxygen reserve compared with propofol during upper gastrointestinal endoscopy: Randomized controlled study

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Objectives: Propofol is commonly used for endoscopic sedation. However, it can induce adverse hemodynamic effects. Remimazolam is known to have a fast onset and short duration comparable to that of propofol, but with fewer effects on hemodynamics. We assessed the Oxygen Reserve Index to verify whether a sedative dose of remimazolam would better preserve oxygenation in the mild hyperoxic range than propofol in sedated patients undergoing diagnostic upper gastrointestinal endoscopy.

Methods: Patients scheduled for diagnostic upper gastrointestinal endoscopy were enrolled. Patients were randomly assigned to either the remimazolam or propofol groups and received 0.1 mg/kg remimazolam or 0.5 mg/kg propofol, respectively. Bolus injections of either 0.05 mg/kg remimazolam or 0.25 mg/kg propofol were added if required. The primary outcome was the prevalence of oxygen reserve depletion, defined as the Oxygen Reserve Index decreasing to 0.00, and hypoxia defined as peripheral oxygen saturation falling to <94%.

Results: Among 69 patients, the incidence of oxygen reserve depletion was significantly higher in the propofol group (65.7% vs. 38.2%, $P = 0.022$). Hypoxia was frequently observed in the propofol group, whereas none was observed in the remimazolam group (11.4% vs. 0%, $P = 0.042$). Additional sedative injections were frequently required to complete endoscopy in the propofol group. None of the patients in the remimazolam group required airway interventions. Nausea was frequent in the propofol group in the recovery room.

Conclusion: Our results indicate that remimazolam is a safe and useful sedative for upper gastrointestinal endoscopy.

Trial registration: This study was registered at Clinicaltrials.gov (NCT05723627) in February 2023.

Key words: benzodiazepine, hypoventilation, oxygen saturation, propofol, sedation

INTRODUCTION

DIAGNOSTIC UPPER GASTROINTESTINAL (UGI) endoscopy is crucial for identifying abnormal lesions in the upper gastrointestinal tract. Sedation during the procedure can help reduce patient discomfort and improve examination quality.[1] However, adverse events such as hypotension or respiratory depression induced by sedatives are rare but inevitable, and the optimal sedation regimen remains disputed.[2]

An ideal sedative for endoscopy should be easy to use and have a rapid onset, short duration, and quick recovery with predictable pharmacokinetic, pharmacodynamic, and safety profiles.[3] To date, commonly used sedatives by endoscopists are propofol and midazolam.[4,5] Propofol is favored for diagnostic endoscopy due to its rapid onset and short duration.[6] However, it is associated with several adverse effects, such as respiratory depression, hypotension, and abuse.[7–9] In contrast, midazolam offers a lower likelihood of respiratory depression or hypotension than propofol, and the presence of its specific antagonist, flumazenil, is a valuable rescue option for clinicians.[6] However, midazolam has a slower onset of action and a longer elimination half-life than propofol, and the potential sedative effect of its active metabolite may lead to slower recovery or resedation in some patients.[10]

Remimazolam, a novel ester-based benzodiazepine, is rapidly metabolized into inactive compounds by nonspecific

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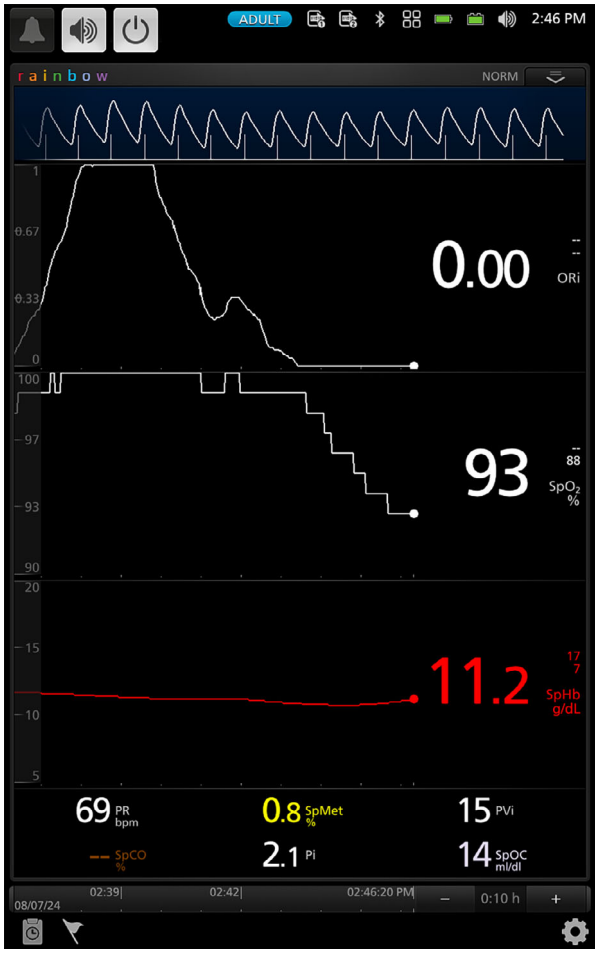

Figure 1 Trends of Oxygen Reserve Index (ORi) and peripheral oxygen saturation (SpO_2) during impending hypoxia. Note that the decline in ORi was initiated first, and SpO_2 started to decrease significantly after ORi reached 0.00.

tissue esterases with a significantly reduced risk of resedation.[11] Remimazolam also has a shorter duration of action than midazolam.[12] With these favorable aspects, remimazolam is routinely used for general anesthesia in the operating room and is gaining popularity for sedation in endoscopic procedures.[13]

The Oxygen Reserve Index (ORi) is a respiratory parameter defined as a value reflecting venous blood oxygen saturation levels.[14] The ORi aids in assessing the oxygenation status in the mild hyperoxia range of PaO_2 100–200 mmHg, which cannot be properly assessed by conventional pulse oximetry.[15] Because the ORi drops towards 0.00 before peripheral oxygen saturation (SpO_2) does, it can be clinically used as an early warning signal for impending hypoxia (Fig. 1).[16] Yet, the ORi is rarely assessed outside operative settings or applied to sedated patients owing to the lack of familiarity. Hence, we assumed that the ORi could effectively detect potential respiratory deterioration induced by sedatives in endoscopy units.

In this study we hypothesized that remimazolam would better preserve oxygenation in the mild hyperoxic range than propofol in patients undergoing diagnostic UGI endoscopy. We examined changes in the ORi and other endoscopic sedation parameters to compare the safety and efficacy of remimazolam and propofol.

METHODS

THIS PROSPECTIVE RANDOMIZED controlled study included patients scheduled for diagnostic UGI endoscopy between April and September of 2023, who adhered to the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines. The study was approved by the Institutional Review Board (IRB, no. 4-2022-1369) of Severance Hospital, Yonsei University Health System, and was registered at Clinicaltrials.gov (NCT05723627). Written informed consent was obtained from all participants, and the study was conducted in accordance with the Ethical Principles for Medical Research Involving Human Subjects outlined in the Helsinki Declaration of 1975 (revised 2013). The inclusion criteria were as follows: (i) American Society of Anesthesiologists (ASA) physical status class I–III; (ii) age 19–80 years; and (iii) undergoing diagnostic UGI endoscopy. The exclusion criteria were: (i) known pulmonary diseases; (ii) obstructive sleep apnea; (iii) hypotension (mean blood pressure <60 mmHg) or hypoxia (SpO_2 < 94%) measured before the endoscopy procedure; and (iv) when baseline ORi did not increase over 0.00 despite preoxygenation.

All enrolled patients were allocated to the study groups according to a randomized sequence provided by Excel (Microsoft, Redmond, WA, USA). Patients were randomly assigned to either the remimazolam or propofol group and blinded to group allocation. Routine monitoring, including electrocardiography, pulse oximetry, and noninvasive blood pressure measurements, was initiated upon arrival at the endoscopy unit.

Evidence indicates a significant correlation between the ORi range of 0.00–1.00 and the PaO_2 range of 100–200 mmHg, which could not be properly assessed by conventional pulse oximetry alone.[15] Therefore, a drop in ORi to 0.00 indicates a potential decline in PaO_2 to <100 mmHg, signaling impending desaturation. To assess the ORi, the Rainbow sensor (Masimo, Irvine, CA, USA) was applied to the index or middle finger. Following our institutional protocol, preoxygenation at a flow rate of

2 L/min was initiated via a nasal cannula for 2 min before sedative injection. During preoxygenation, we ensured that the ORi value increased from 0.00 and plateaued for at least 30 s to assess a stable baseline ORi value. Depending on the assigned group, patients received an intravenous injection of either 0.1 mg/kg remimazolam over 1 min or 0.5 mg/kg propofol. Sedation was performed by an anesthesiologist to ensure immediate intervention in cases of adverse events.

Endoscopy was initiated when the sedation level reached a Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S; Table S1) score of 3 or 4. In case of insufficient sedation, either 0.05 mg/kg remimazolam or 0.25 mg/kg propofol was added per requirement according to the group allocation.

When hypoxia defined as SpO_2 <94% occurred, airway interventions such as increasing the oxygen flow rate, chin lift, or facial oxygen mask application were considered. Hypertension was defined as a mean blood pressure increase of >20% from the baseline. Hypotension was defined as mean blood pressure decrease by >20% from baseline or <60 mmHg. In case of hypotension, ephedrine, phenylephrine, or norepinephrine injections were considered. Tachycardia and bradycardia were defined as heart rates >120 beats/min and <50 beats/min, respectively.

Endoscopy duration was defined as the time from sedative injection to endoscope withdrawal. Immediately after completing the examination, the endoscopist assigned a satisfaction score considering both the depth of sedation and ease of examination. Patients were transferred to the recovery room (RR) and assessed for nausea, dyspnea, dizziness, and pain. Discharge from the RR was determined based on a Modified Aldrete Score ≥9 (Table S2). Before discharge, all patients were asked to rate their overall satisfaction with the sedation. The overall procedure time, defined as the time from the initial sedative injection to RR discharge, was assessed.

Hemodynamic data including heart rate, blood pressure, and SpO_2 were measured at the following time points: before sedation (baseline), immediately after endoscope insertion (T1), 3 min after T1 (T2), end of examination (T3), entrance into RR (R1), 5 min after R1 (R2), and discharge from RR (R3).

The primary outcome was the prevalence of oxygen reserve depletion defined as ORi decreasing to 0.00 and hypoxia defined as SpO_2 <94%. Other outcomes included procedural- and sedation-related outcomes, adverse events, and side-effects.

The sample size was calculated based on the results of a pilot study conducted on two groups of 20 patients. Of the 40 patients studied, 15 in the propofol group (75%) and six in the remimazolam group (30%) experienced an ORi decrease to 0.00. GPower (version 3.1.9.2; Brunsbüttel, Germany) estimated that 29 patients were required in each group, with a power of 80% and a significance level of 0.05. Accounting for a 20% dropout rate, a total of 70 patients, with 35 patients in each group, were required for this study.

The unpaired Student's *t*-test was used to analyze continuous variables, and the Mann–Whitney *U*-test was used to analyze variables that did not meet normality. The χ^2-test or Fisher's exact test was used to compare categorical variables between the groups. Repeated variables were analyzed using a linear mixed model with groups and time and the interaction between groups and time as a fixed effect. Post-hoc analysis with Bonferroni correction for within-group comparisons was performed for multiple comparisons if required. SPSS version 20.0 (IBM, Armonk, NY, USA) statistical software was used for data analysis and $P < 0.05$ was considered statistically significant.

RESULTS

SEVENTY PATIENTS SCHEDULED for diagnostic UGI endoscopy were enrolled in this study (Fig. 2). All patients completed the procedure without sedation failure; however, one patient in the remimazolam group was excluded because the ORi did not increase from 0.00 despite preoxygenation. Hence, the data from 69 patients were analyzed.

The baseline characteristics, including comorbidities and prediagnosed UGI diseases, were similar between the groups (Table 1). The data assessed in the endoscopy units are presented in Table 2. Additional sedative injections were required more frequently in the propofol group than in the control group. The incidence of oxygen reserve depletion was significantly higher in the propofol group (65.7% vs. 38.2%, $P = 0.022$). Hypoxia was frequently observed in the propofol group, whereas none was observed in the remimazolam group (11.4% vs. 0%, $P = 0.042$). Tachycardia was also more frequent in the propofol group (22.9% vs. 5.9%, $P = 0.045$), but incidences of hypertension, hypotension, and bradycardia were similar between the groups. Endoscopy duration and satisfaction scores marked by the endoscopists did not differ between the groups. The trends in the hemodynamic variables and MOAA/S are shown in Figure 3. Although the Mann–Whitney *U*-test showed differences between the SpO_2 of the two groups at T1 and T3 (Fig. 2), the linear mixed model analysis did not show significant differences among them in the trends of hemodynamic parameters (Table S3).

The adverse events during endoscopy and interventions performed by the attending anesthesiologist are listed in Table 3. The incidence of events interfering with endoscopy, such as hiccups, belching, spontaneous movements, and the need for physical restraint, was comparable between the

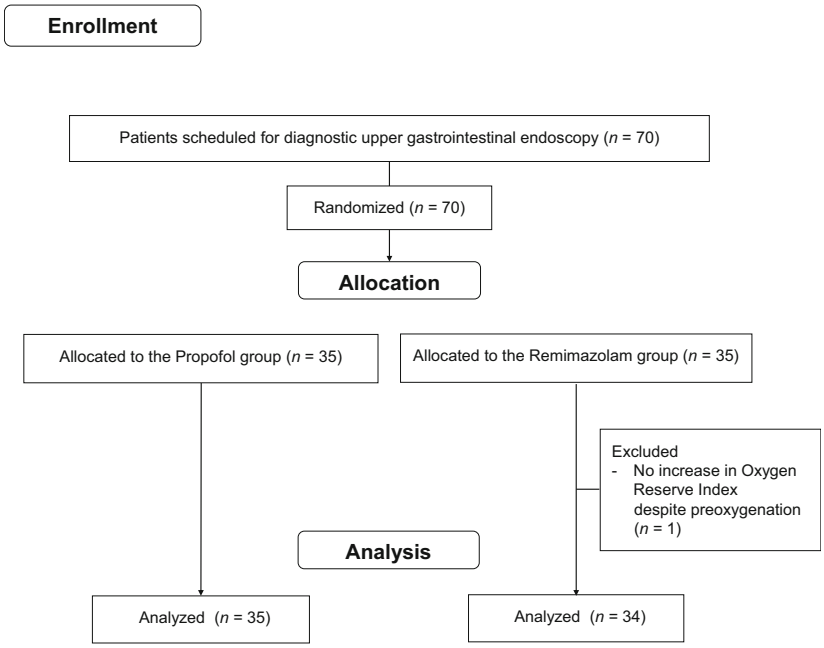

Figure 2 Patient enrollment.

Table 1 Baseline characteristics of the patients

	Propofol group (n = 35)	Remimazolam group (n = 34)	P-value
Age (years)	61.8 ± 13.7	64.8 ± 11.5	0.319
Sex (M/F, n)	17 (48.6)/18 (51.4)	21 (61.8)/13 (38.2)	0.271
Height (cm)	163.3 ± 11.2	164.5 ± 8.7	0.636
Weight (kg)	60.20 [53.50, 78.00]	66.20 [54.90, 75.00]	0.540
Body mass index (kg/m^2)	23.80 ± 3.33	24.29 ± 3.59	0.555
Hypertension	11 (31.4)	18 (52.9)	0.070
Diabetes mellitus	8 (22.9)	8 (23.5)	0.947
Gastritis	16 (45.7)	13 (38.2)	0.529
Gastric cancer	16 (45.7)	19 (55.9)	0.398
Esophageal cancer	2 (5.7)	2 (5.9)	0.976
Liver cirrhosis	1 (2.9)	0 (0.0)	0.321
ASA classification			0.992
I	6 (17.1)	6 (17.6)	-
II	17 (48.6)	16 (47.1)	-
III	12 (34.3)	12 (35.3)	-

Data are presented as mean ± standard deviation, number (%), or median [interquartile range].
ASA, American Society of Anesthesiologists; F, female; M, male.

groups. Regarding anesthetic interventions, three patients in the propofol group were treated with ephedrine injection, increased oxygen flow, or the chin lift maneuver, whereas none in the remimazolam group required such maneuvers.

The RR data are presented in Table 4. Adverse events reported in RR were more frequent in the propofol group, which primarily resulted from a higher incidence of nausea (22.9% vs. 2.9%, P = 0.014). There were no significant differences in procedural recall or patient satisfaction scores. The remimazolam group required a significantly longer recovery time from the end of endoscopy to full alertness (9.0 min [7.0 min, 15.0 min] vs. 14.0 min [12.0 min, 17.0 min], P = 0.005). However, the RR length of stay and overall procedure time were similar between the groups.

Table 2 Data assessed in the endoscopy unit

	Propofol group (n = 35)	Remimazolam group (n = 34)	P-value
Incidence of sedative addition (n)	23 (65.7)	11 (32.4)*	0.006
Once	17 (48.6)	8 (23.5)*	0.030
Twice or more	6 (17.1)	3 (8.8)	0.305
Total sedative dose (mg)	60 [50, 70]	6.0 [5.0, 7.0]	N/A
Baseline ORi	0.26 [0.18, 0.40]	0.28 [0.21, 0.49]	0.410
Hemodynamic events			
Incidence of ORi = 0.00 (n)	23 (65.7)	13 (38.2)*	0.022
Incidence of SpO_2 < 94% (n)	4 (11.4)	0 (0.0)*	0.042
Hypertension	11 (31.4)	14 (41.2)	0.400
Hypotension	5 (14.3)	6 (17.6)	0.703
Tachycardia	8 (22.9)	2 (5.9)*	0.045
Bradycardia	1 (2.9)	1 (2.9)	0.983
Endoscopy duration (min)	4.0 [4.0, 5.0]	5.0 [4.0, 5.0]	0.732
Endoscopist satisfaction score			0.215
High	15 (42.9)	18 (52.9)	-
Medium	17 (48.6)	10 (29.4)	-
Low	3 (8.6)	6 (17.6)	-

Data are presented as number (%) or median [interquartile range].
N/A, Not Applicable; ORi, Oxygen Reserve Index; SpO_2, peripheral oxygen saturation.
*P < 0.05 vs. propofol group.

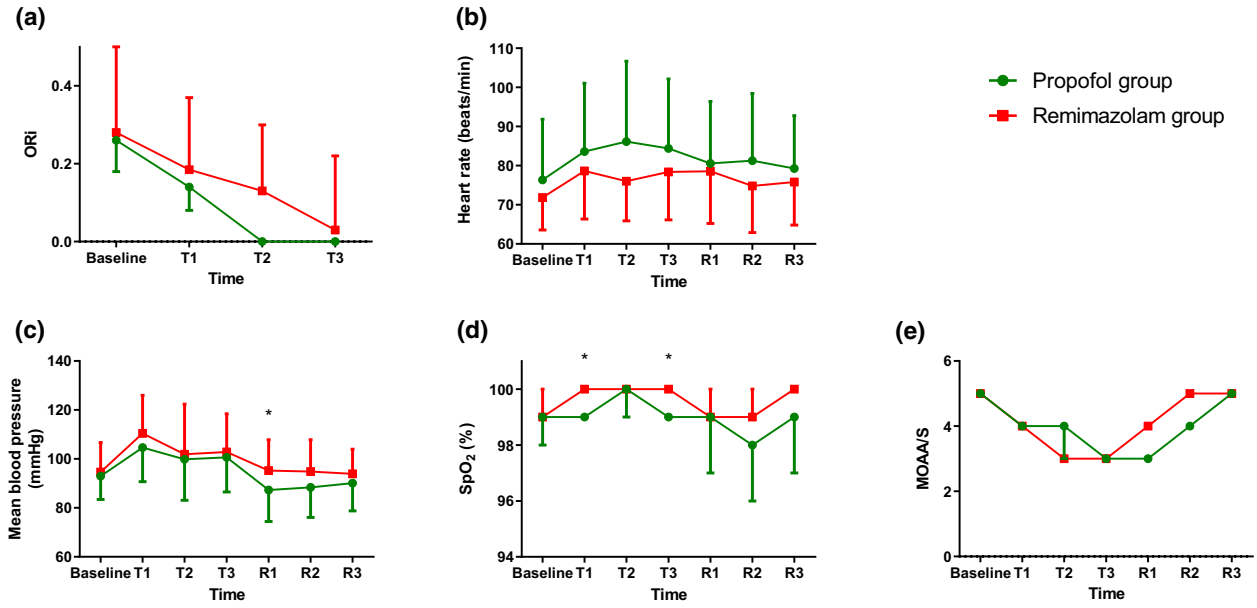

Figure 3 Trends of hemodynamic variables and sedation scale. (a) Oxygen Reserve Index (ORi). (b) Heart rate. (c) Mean blood pressure. (d) Peripheral oxygen saturation (SpO_2). (e) Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S). Error bars represent the interquartile range in panels (a,d,e) and standard deviation in panels (b,c). Baseline, before sedation; R1, entrance into the recovery room; R2, 5 min after R1; R3, discharge from the recovery room; T1, immediately after endoscope insertion; T2, 3 min after T1; T3, end of examination. *P < 0.05 vs. propofol group.

DISCUSSION

TO THE BEST of our knowledge, this is the first study to evaluate the ORi during sedation in endoscopic procedures. We observed that the incidence of oxygen reserve depletion with remimazolam was significantly lower than that with propofol during diagnostic UGI endoscopy. Remimazolam was also advantageous over propofol in terms of a lower requirement for additional doses during the procedure and fewer nausea incidences in the RR.

Although propofol is favored by endoscopists owing to its rapid onset and short sedative duration, its potential cardiorespiratory depressive effect can pose a significant threat to patient safety.[17] In addition, feelings of well-being or even euphoria after propofol injection have been identified as a potential cause of drug abuse.[8,9] Therefore, there is a need for safer sedative options for endoscopy, with remimazolam emerging as a promising candidate. Recently, the safety and efficacy of remimazolam and propofol have been comparatively assessed[18]; however, few studies have focused on their potential adverse effects on respiration. Previous studies defined respiratory depression as reduced respiratory rate or SpO_2 <90%, but it is noteworthy that anesthetic doses of sedatives combined with opioids were administered in those studies.[19,20] Hence, we presumed that more stringent criteria are required to sensitively detect respiratory depression in endoscopic procedures that require light sedation. Rather than counting the respiratory rate, which may be easily interrupted by involuntary movements, we assessed the ORi to accurately measure the potential respiratory depression induced by sedatives. In addition, we elevated the hypoxic SpO_2 threshold from 90% to 94%, as evidently, 95% of hypoxemic PaO_2 measurements occur in patients with an SpO_2 <94%.[21]

Table 3 Adverse events and interventions during endoscopy

	Propofol group (n = 35)	Remimazolam group (n = 34)	P-value
Events interfering with the procedure			
Hiccups	6 (17.1)	6 (17.6)	0.956
Belching	3 (8.6)	8 (23.5)	0.090
Spontaneous movements	19 (54.3)	16 (47.1)	0.548
Requiring physical restraint	1 (2.9)	3 (8.8)	0.289
Any of the above	19 (54.3)	20 (58.8)	0.704
Interventions by anesthesiologist			
Ephedrine use	1 (2.9)	0 (0.0)	0.321
Increase in oxygen flow	1 (2.9)	0 (0.0)	0.321
Chin lift	2 (5.7)	0 (0.0)	0.157
Any of the above	3 (8.6)	0 (0.0)	0.081

Data are presented as number (%).

Table 4 Data assessed in the recovery room (RR)

	Propofol group (n = 35)	Remimazolam group (n = 34)	P-value
Adverse events			
Nausea	8 (22.9)	1 (2.9)*	0.014
Dyspnea	1 (2.9)	0 (0.0)	0.321
Dizziness	5 (14.3)	5 (14.7)	0.960
Pain	1 (2.9)	0 (0.0)	0.321
Any of the above	13 (37.1)	5 (14.7)*	0.034
Procedural recall			0.321
No recall	26 (74.3)	30 (88.2)	-
Partial recall	6 (17.1)	3 (8.8)	-
Full recall	3 (8.6)	1 (2.9)	-
Patient satisfaction score			0.517
High	17 (48.6)	12 (35.3)	-
Medium	15 (42.9)	19 (55.9)	-
Low	3 (8.6)	3 (8.8)	-
Time from the end of endoscopy to fully alert (min)	9.0 [7.0, 15.0]	14.0 [12.0, 17.0]*	0.005
Length of stay in RR (min)	13.0 [11.0, 21.0]	15.0 [10.75, 20.50]	0.596
Overall procedure time†	19.0 [16.0, 25.0]	22.0 [17.0, 28.0]	0.158

Data are presented as number (%) or median [interquartile range].
*P < 0.05 vs. propofol group.
†Time from initial sedative injection to RR discharge.

The additional warning time provided by ORi monitoring could be vital for enabling timely airway interventions.[16,22,23] In our study, a warning signal from ORi was more frequent in the propofol group, followed by more frequent hypoxic events. Hence, our results suggest that remimazolam can more reliably maintain a patient's oxygenation levels within a safe range.

It should be noted that among the patients whose ORi showed an early warning signal of hypoxia, only a small number required airway intervention by the attending anesthesiologist. We presume that this may be attributable to the low dose of sedatives used for light sedation. To our knowledge, the guidelines suggest individual titration of sedative doses, but seldom provide clear dosage recommendations based on patient weight.[24,25] Considering the short and noninvasive nature of diagnostic UGI endoscopy, we empirically set the initial dose of propofol at 0.5 mg/kg and that of remimazolam at 1.0 mg/kg, which are comparable to or less than those reported in other clinical studies.[26] We intended to minimize adverse hemodynamic effects by injecting a low initial dose. Indeed, no significant differences in heart rate, mean blood pressure, or SpO_2 trends were observed in our linear mixed model analysis. Although low sedative doses often result in inadequate sedation, which may be potentially linked to the few cases of tachycardia in the propofol group, the judicious use of supplemental sedatives enabled successful completion of the procedure in all patients without sedation failure. The stability of anesthesia can be inferred from the need for supplemental sedatives and adverse hemodynamic events, as detailed in Table 2. It is noteworthy that small doses of propofol were sufficient to induce hypoventilation in 65.7% of patients, underscoring its potent respiratory depressant effects. Conversely, 0.1 mg/kg remimazolam provided adequate sedation while minimally impacting respiration.

Although some studies report that remimazolam has a slower onset of action than propofol,[5,12] there was no significant difference in endoscopy duration between the two groups. However, the recovery time to become fully alert after remimazolam sedation was approximately 5 min longer than that after propofol sedation, most likely resulting from the longer decrement time of the effect-site concentration of remimazolam.[27] Nonetheless, no significant difference was observed in the length of stay in the RR or overall procedure time, and it is noteworthy that flumazenil was not administered to any of the patients in the remimazolam group to reduce recovery time or to reverse respiratory depression. Our results suggest that, although remimazolam requires a slightly longer time for cognitive return than propofol, it does not adversely affect the patient turnover rate, which is consistent with the results of a previous study.[28] Additionally, satisfaction scores assessed by the endoscopists and patients were comparable between the groups, implying that both remimazolam and propofol provided comparable quality of sedation.

The incidence of adverse events in the RR was significantly lower in the remimazolam group than in the propofol group, primarily driven by a reduced incidence of nausea. Although the subhypnotic dose of propofol is known to be similarly beneficial in preventing postoperative nausea compared to midazolam,[29] no study has yet compared the antiemetic efficacy of such doses of propofol and remimazolam during endoscopic procedures. Our results suggest that low-dose remimazolam is superior to propofol in terms of reducing postprocedural nausea, thus offering a better recovery profile.

This study has a few limitations. First, it was conducted at a single facility with a limited population. Second, owing to the difference in administration methods of remimazolam and propofol, blinding the participating anesthesiologist was not feasible. Third, although invasive blood pressure monitoring would have helped observe the antihypertensive effects of sedatives during endoscopic insertion, we could not continuously assess blood pressure. Placing an arterial line is inappropriate for short diagnostic endoscopies, and should only be considered in more invasive endoscopic procedures with longer procedure times. Fourth, we excluded morbid patients, such as those with known respiratory diseases or obstructive sleep apnea. Therefore, it is desirable to confirm the efficacy of remimazolam in high-risk patients. However, because this was the first study to compare the effectiveness of remimazolam and propofol, we excluded high-risk patients. We intend to conduct future studies to evaluate the efficacy of remimazolam treatment in this cohort. Finally, the ORi could not be monitored in the RR owing to a lack of a compatible monitoring system, which would have been informative regarding the oxygenation status during the recovery period.

In conclusion, the sedative dose of remimazolam had minimal adverse effects on respiration, with less requirement for additional doses, and a superior antiemetic effect compared to propofol. Our results indicate that remimazolam is a safe and useful sedative for UGI endoscopy.

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CONFLICT OF INTEREST

AUTHORS DECLARE NO conflict of interest for this article.

ETHICS STATEMENT

APPROVAL OF THE research protocol by an Institutional Reviewer Board: The study was approved by the Institutional Review Board (IRB, no. 4-2022-1369) of Severance Hospital, Yonsei University Health System (Seoul, Korea), in December 2022.

Informed Consent: Written informed consent was obtained from all participants involved in the study.

Registry and the Registration No. of the study/trial: This study was registered at Clinicaltrials.gov (NCT05723627) in February 2023.

Animal Studies: N/A.

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SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found in the online version of this article at the publisher's web site.

Table S1 Modified observer assessment of alertness/sedation scale.

Table S2 Modified Aldrete Score.

Table S3 Linear mixed-model analysis of hemodynamic data during endoscopy.