Trials

STUDY PROTOCOL

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Remimazolam versus midazolam for sedation in diagnostic upper gastrointestinal endoscopy: study protocol for a randomized controlled trial

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Abstract

Background Remimazolam is a new alternative drug combining the efficacy and safety advantages of midazolam and propofol. However, studies comparing remimazolam with midazolam in diagnostic upper gastrointestinal endoscopy are insufficient. The purpose of this study was to prove the efficacy and safety of remimazolam in diagnostic upper gastrointestinal endoscopy compared with midazolam.

Methods This study is a randomized, controlled, multicenter trial. Participants who are to receive diagnostic upper gastrointestinal endoscopy are enrolled and randomly assigned to the remimazolam or midazolam group (control group) at a 1:1 ratio. Remimazolam is given (with an initial 5 mg plus an additional 2.5 mg, maximum 5 times) in the remimazolam group for endoscopic sedation and midazolam is given (with an initial 2 mg plus an additional 1~2 mg, maximum 5 times) in the control group. Flumazenil can be given at the discretion of the investigator. Vital signs, level of consciousness, and adverse events are assessed from the administration of sedatives to the full recovery of consciousness. The primary endpoint is total procedure time, which is defined as the time from the first administration of sedatives to discharge. The secondary endpoints include the success rate of sedation, recovery time, induction time, total endoscopy time, discharge time, sedation time, incidence of hypotension, respiratory depression, tachycardia, bradycardia, participant satisfaction, and paradoxical response incidence.

Discussion The results of this trial are expected to prove the superior efficacy of remimazolam with favorable safety. Based on the results, a sedation method using remimazolam would be applied preferentially for diagnostic upper gastrointestinal endoscopy in clinical practice.

Trial registration Clinicaltrials.gov NCT05836545. Registered on April 19, 2023

Keywords Endoscopic sedation, Remimazolam, Midazolam, Efficacy, Safety, Total procedure time

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Background

Conscious sedation during endoscopy, also known as endoscopic sedation, uses sedatives to reduce patient anxiety or discomfort, with the ultimate goal of creating an amnesic effect to ensure an accurate endoscopic examination and patient satisfaction during the procedure [1, 2]. In addition to controlling patient anxiety and discomfort, sedation also serves to maximize patient comfort and minimize the risk of drug-related side effects [1, 2]. The use of sedatives during endoscopy has increased in Korea, and endoscopic sedation has become a common practice in many medical centers.

In clinical practice, benzodiazepines and opioids are commonly used for conscious sedation, and the most common agents are midazolam and propofol [3]. Midazolam is a member of the benzodiazepine family and the drug of choice for most endoscopists due to its rapid onset of action, short duration of action, and amnesic properties [3]. However, midazolam can have adverse effects such as respiratory depression and paradoxical reactions sometimes leading to fatal outcomes [3]. Therefore, caution and proper monitoring are required after administration. Propofol has the advantages of no cumulative effects, and its short half-life due to rapid metabolism and excretion enables rapid recovery when discontinued [4]. However, propofol should be used with caution because no antagonist is available in cases of adverse events such as respiratory decompression or shock [1].

Remimazolam is a new alternative drug that combines the advantages of traditional sedatives such as midazolam and propofol [5]. Remimazolam has the following advantages over midazolam: little respiratory depression, little effect on hemodynamics, rapid onset of action, short half-life, and no accumulation in the body after long-term infusion, enabling rapid recovery [5]. Therefore, remimazolam might be a promising sedative that can shorten the overall procedure time. In addition, while there is no antagonist to reverse sedation after the administration of propofol, remimazolam has an antagonist, flumazenil, that can cause the immediate reversal of sedation, which is a major advantage of remimazolam in terms of safety [5].

Several phase III studies have proved that remimazolam is an effective agent for sedation induction and maintenance compared to traditional agents in colonoscopy and bronchoscopy with respect to safety and efficacy [6–11]. However, to the best of our knowledge, studies comparing remimazolam with traditional benzodiazepines like midazolam in diagnostic upper gastrointestinal endoscopy are insufficient yet. Therefore, we planned this randomized controlled trial to prove the efficacy and safety of remimazolam in diagnostic upper gastrointestinal endoscopy compared with midazolam.

Methods/design

Study design and ethical considerations

This study is a multicenter, prospective, randomized, single-blind, parallel-controlled clinical trial conducted for the purpose of comparing and analyzing the efficacy and safety of sedation with midazolam or remimazolam in patients who receive diagnostic upper gastrointestinal endoscopy. It is designed as a superiority trial. All participating institutions are teaching hospitals with a College of Medicine in Korea. This study was approved by the Institutional Ethics Review Board (IRB) of Samsung Medical Center, Sungkyunkwan University School of Medicine (IRB No. 2022-08-031), and then by the IRB of each institution participating in this study (IRB No. 20–2022-90 in Seoul National University Boramae Medical Center; IRB No. 2022-09-010 in Dongguk University Ilsan Hospital; IRB No. 2022-09-002-001 in Chungnam National University School of Medicine; IRB No. SEUMC 2022-11-013-002 in Ewha Womans University Seoul Hospital; IRB No. 2022-08-059 in Yeungnam University College of Medicine; and IRB No. 2022-11-012-005 in College of Medicine, Chosun University). The health and human rights of subjects will be prioritized based on the Declaration of Helsinki, and voluntary written consent will be obtained from all subjects before they enter the clinical study. All participants who meet the inclusion criteria and agree to participate will receive an information sheet and consent form. Before signing the informed consent form, participants can discuss the study details with the investigators, ask questions, and take as much time as they need to consider their decision. The investigators conducting the study will obtain informed consent from the participants. All enrollment in the study will be subject to obtaining a signed consent form before the initiation of study procedures. Records identifying the subject's identity will be kept confidential.

Inclusion criteria

Participants who meet the following requirements are eligible for enrollment: (1) scheduled for a sedative upper gastrointestinal endoscopy for diagnostic purposes, (2) aged 19 to 60 years; (3) American Society of Anesthesiologists (ASA) score ≤ 2 (Table 1) [1]; (4) body mass index (BMI) greater than 18.5 kg/m^2 and less than 30 kg/m^2; and (5) capable of understanding the information and signing a written consent voluntarily after listening to an explanation of the purpose, methods, and effects of the study.

Table 1 American Society of Anesthesiologists (ASA) score

Scores	Physical status
I	Normal healthy patient
II	Patient with mild systemic disease that does not limit their activities
III	Patient with moderate or severe systemic disease which does limit their activities
IV	Patient with severe systemic disease that is a constant potential threat to life
V	The patients is morbid and is at a substantial risk of death within 24 h (with or without procedure)

Table 2 Mallampati Score

Class	Visualization
1	Complete visualization of the soft palate
2	Complete visualization of the uvula
3	Visualization of only the base of uvula visible
4	Soft palate is not visible at all

Exclusion criteria

Participants with any of the following conditions are excluded: (1) suspected pathologic conditions of the gastrointestinal tract that may require therapeutic endoscopy; (2) a history of breathing problems during sedation (e.g., chronic obstructive pulmonary disease, breathing disorders due to cerebrovascular disease and musculoskeletal disorders, individuals with tracheal cannulas); (3) considered difficult to maintain an airway (Mallampati score ≥ 3, Table 2) [1]; (4) pre-randomization systolic blood pressure greater than 160 mmHg or less than 90 mmHg; (5) uncontrolled hypertension; (6) acute narrow-angle glaucoma; (7) severe hepatic dysfunction or chronic kidney disease; (8) a history of drug or alcohol abuse in the past year; (9) hypersensitivity to other benzodiazepine medications or components of remimazolam (e.g., dextran), (10) hypersensitivity to any of the components of midazolam; (11) sleep apnea syndrome, (12) genetic conditions, such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption; (13) pregnant or breastfeeding women, or women with a positive pregnancy test at screening; (14) administered any drug in other clinical trials within 1 month prior to screening; (15) informed consent could not be obtained; and (5) considered to be difficult to perform this clinical trial when judged by the principal investigator.

Randomization

The screening of participants for eligibility is performed during the screening period (within 4 weeks before randomization), and informed consent will be obtained from the participants during this screening period. The eligible participants will be randomized within 15 min of the start of the endoscopic procedure in a 1:1 fashion to receive remimazolam or midazolam (control group). Block randomization will be performed using Random Allocation Software version 1.0.0. A person who is not involved in the study will create random numbers before the first subject enrolls after IRB approval. The random numbers will be kept in sealed envelopes in the order of their creation. An independent hospital staff member will prepare the sealed envelopes to ensure the concealment of the allocation sequence. The numbers will be handed over to assistants (independent investigators). After randomization, the treatment method will be single-blinded (only blinded to participants).

Administration of sedative agents and assessment of participants

Remimazolam is given before the start of the endoscopic procedure in the remimazolam group. The administration of remimazolam is performed at an initial dose of 5 mg, and an additional 2.5 mg can be given according to the sedative state at an interval of 2 min (maximum 5 times during 15 min). Midazolam is given before the start of the endoscopic procedure in the midazolam group (control group). The administration of midazolam is performed at an initial dose of 2 mg, and an additional 1~2 mg can be given according to the sedative state at an interval of 2 min (maximum 5 times during 15 min). Other sedative agents such as propofol are not permitted to be given even in case of insufficient sedation after administration of remimazolam or midazolam.

Flumazenil, a benzodiazepine antagonist, can be given if consciousness does not recover even more than 30 min after the discontinuation of the sedative, at the discretion of the investigator. Flumazenil is administered at a dose of 0.2 mg, and an additional 0.1 mg can be given at an interval of 1 min (maximum dose of 1 mg).

During the period from the administration of sedatives to the full recovery of consciousness, continuous monitoring of heart rate and oxygen saturation is performed,

and supplemental oxygen can be applied if required. The assessment of vital signs (systolic and diastolic blood pressure [SBP and DBP], pulse rate, respiration rate, and oxygen saturation) is performed before the administration of sedatives, at the start of the endoscopic procedure, 3 min after the administration of sedatives, and then every 5 min until discharge. The assessment of consciousness is performed before the administration of sedatives, at the start of the endoscopic procedure; 1, 1.5, 2, 2.5, 3, 4, and 5 min after the administration of sedatives; every 2 min until the full recovery of consciousness, and then every 5 min until discharge. The Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) is used to assess consciousness (Table 3) [2]. The full recovery of consciousness is defined as an MOAA/S score of 5 on 3 consecutive times. The assessment of adverse events is performed every 5 min until discharge.

After the full recovery of consciousness, an assessment is performed using the Aldrete Scoring System (Table 4) [2]. Participants can be discharged from the institution when their Aldrete score is more than 9. At the time of discharge, the assessment of participant satisfaction is performed by providing a questionnaire to the participants. Participant satisfaction will be assessed in 4 categories: overall satisfaction, comfort level, willingness to recommend, and satisfaction compared to previous endoscopic procedures.

Table 3 Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S)

Scores	Score description
5	Responds readily to name spoken in normal tone (alert)
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding of shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Outcomes

The primary endpoint is total procedure time, which is defined as the time from the first administration of sedative to discharge. The secondary endpoints include the success rate of sedation (<1> completion of the whole endoscopy procedure; <2> no requirement for an alternative and/or rescue sedative; <3> administered up to a maximum of 5 supplemental doses within 15 min after the initial dose) [6, 12], recovery time (from last administration of sedatives to full recovery of consciousness), induction time (from the first administration of sedatives to adequate sedation [MOAA/S score of 3 or less]), total endoscopy time (from endoscope insertion to endoscope retrieval), discharge time (from endoscope retrieval to discharge), sedation time (from the first administration of sedatives to full recovery of consciousness), incidence of hypotension (SBP $\leq$ 80 mmHg, DBP $\leq$ 40 mmHg, or SBP or DBP decreased by 20% or more from baseline), respiratory depression (oxygen saturation < 90% for more than 1 min), tachycardia (heart rate > 100/min or 20% increase from baseline), or bradycardia (heart rate < 60/min or 20% decrease from baseline), participant satisfaction (questionnaire), and the incidence of a paradoxical response.

Table 4 Aldrete Scoring System

Post-Sedation Recovery Scorecard (Recovery Score)		
Reflexes	Can move 4 of their limbs on command or voluntarily	2
	Can move 2 or more limbs on command or voluntarily	1
	Unable to move all limbs on command or voluntarily	0
Breathing	Deep breathing and coughing features	2
	Shortness of breath or restricted breathing movements	1
	Apnea	0
Circulation	Within ±20% of pre-anesthesia/sedation blood pressure	2
	20–50% of pre-anesthesia/sedation blood pressure	1
	50% or more of pre-anesthesia/sedation blood pressure	0
Consciousness	Full recovery	2
	Eyes open when called	1
	Unresponsive	0
Skin Color	Pink	2
	Pale, dull, mottled, jaundiced	1
	Cyanosis	0

Planned number of participants and period

The primary objective of this study is to determine the superiority of remimazolam's total procedure time compared to midazolam. The primary hypothesis is that the total procedure time will be shorter in the remimazolam group compared to the midazolam group (control group).

In a previous study [13], the mean total procedure time in the midazolam group was 48.3 min, and we expect the mean total procedure time in the remimazolam group to be 7.245 min less than the midazolam group (15% less than the midazolam group). Therefore, we set an effect size of 7.245 min. Since the standard deviation (SD) of the total procedure time was not presented in the previous study, we made the following assumptions. Assuming that the total procedure time follows a normal distribution and the SD of the total procedure time in the midazolam group is the largest value, the SD of the total procedure time was set to 12.075 (calculated as 48.3–4*SD = 0) and was assumed to be the same in both groups. When testing the primary hypothesis with a two-sample *t*-test at a one-sided significance level of 2.5% and a power of 90%, the required number of participants was calculated to be 120 (60 in each group) using PASS 22.0.2 software. Sixty-six participants will be randomized to each group to allow for a possible 10% dropout rate. The sample size calculation process is presented in Fig. 1.

A total of 132 participants will be enrolled for 10 months. Screening, allocation, intervention (administration of sedatives), and monitoring will be performed for each participant during the study period. Follow-up will be terminated after discharge from the institution. The schedule of enrollment, interventions, and assessments is summarized in Fig. 2.

Adverse events

Adverse events refer to undesirable and unintended signs, symptoms, or illnesses that occur after the procedure. Adverse events related to endoscopic sedation are harmful and unintended reactions that cannot be excluded from having a causal relationship with the sedatives used in this study. The types of adverse events include hypoxemia, hypotension, tachycardia, bradycardia, hypertension, arrhythmia, aspiration, and paradoxical reaction [14]. Significant adverse events (SAE) include those that cause death or threaten life, require an extension of hospitalization or length of stay, or cause disability, impairment of function, or congenital malformations. Even if not included in the circumstances listed above, a medical condition that is likely to have a significant impact on the patient's health and well-being is regarded as an SAE by the medical judgment of the investigators and relevant experts. All adverse events will be recorded in the case report form (CRF), and SAEs will be reported to the IRB as well as on the Clinicaltrials.gov database and managed appropriately. The IRB will decide whether to stop or continue the study when SAEs occur.

Two-Sample T-Tests Assuming Equal Variance

Numeric Results for an Equal-Variance T-Test

Solve For: Sample Size
Difference: δ = μ1 - μ2
Hypotheses: H0: δ ≤ 0 vs. H1: δ > 0

Target Power	Actual Power	N1	N2	N	μ1	μ2	δ	σ	Alpha
0.9	0.90312	60	60	120	48.3	41.055	7.245	12.075	0.025

Target Power	The desired power value (or values) entered in the procedure. Power is the probability of rejecting a false null hypothesis.
Actual Power	The power obtained in this scenario. Because N1 and N2 are discrete, this value is often (slightly) larger than the target power.
N1 and N2	The number of items sampled from each population.
N	The total sample size. N = N1 + N2.
μ1 and μ2	The assumed population means.
δ	The difference between population means at which power and sample size calculations are made. δ = μ1 - μ2.
σ	The assumed population standard deviation for each of the two groups.
Alpha	The probability of rejecting a true null hypothesis.

Fig. 1 The sample size calculation process

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT**	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	t_6
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
INTERVENTIONS:								
Midazolam group			←	—	—	→		
Remimazolam group			←	—	—	→		
ASSESSMENTS:								
Vital signs	X	X	X	X	X	X	X	X
Level of consciousness		X	X	X	X	X	x	X
Adverse events		X	X	X	X	X	x	X
Laboratory exam	X							

Fig. 2 Schedule of enrollment, interventions, and assessments

Data management

Information on each participant will be collected from enrollment to discharge. Double checks for data values will be performed by a trained research assistant after completing the final data collection. The final data will be assessed by the investigators on the research team. An interim analysis is not planned. For those who die during the study, only data before death will be included in the analysis.

Data monitoring

The study will be supervised by the Data and Safety Monitoring Board (DSMB), which consists of physicians, ethicists, medical statisticians, and a clinical manager. Their responsibility is to oversee the study and audit the trial conduct. The frequency for auditing by the DSMB is once every 6 weeks, and the procedure for auditing will be independent of investigators and the sponsor. The DSMB will thoroughly examine safety data, processes, and clinical effectiveness reports to identify any potential issues, discrepancies, or areas for improvement. At each time of auditing, the DSMB will determine if the clinical trial should continue. The primary investigator at Samsung Medical Center will receive its feedback, and then, the primary investigator will share the feedback with all investigators at each institution.

Monitoring will be conducted throughout the trial, and any adverse events will be recorded. As mentioned earlier, all adverse events will be recorded in the CRF, and SAEs will be reported to the IRB as well as the Clinicaltrials.gov database and managed appropriately. The IRB will decide whether to stop or continue the study when SAEs occur.

The research center for the trial will keep the medical records of the participants, such as the CRF, fully secured and stored. The confidentiality of personal data gathered during the study will be maintained, and all data will be saved on an encrypted computer located in the research center. Access to this computer will only be granted to authorized researchers working on the trial, and the data will only be used for the purposes of the trial and not for any other reasons.

Plans for communicating important protocol modifications

Any changes to the trial protocol will first be discussed at an investigator meeting, and based on the discussion, the proposed changes will be approved or rejected. If the meeting approves the proposal, a new version of the trial protocol will be prepared by the primary investigator at Samsung Medical Center and reviewed and filed with the IRB at Samsung Medical Center. If the IRB approves the trial protocol modifications, the primary investigator at Samsung Medical Center will share the modified trial protocol by both investigator meeting and upload of the protocol to an investigator website. Any modifications of the trial protocol will be also reported to the DSMB.

Statistical analysis

Statistical analyses will be based on the intention-to-treat (ITT) population. Missing data imputation will be used to evaluate the robustness of the primary endpoint analysis. The primary imputation method will be the last observation carried forward (LOCF). Statistical analyses will be performed using the Student's *t*-test or Wilcoxon's rank-sum test for continuous variables and the chi-squared or Fisher's exact test for categorical variables.

A one-sided test will be performed using the Student's *t*-test or Wilcoxon rank sum test to determine the superiority of the remimazolam group in the primary endpoint (total procedure time), recovery time, discharge time, and sedation time. If the one-sided *P*-value for each variable is less than 0.025, it will be concluded that the remimazolam group is superior to the control group in each variable.

Total endoscopy time, induction time, and participant satisfaction will be analyzed using the Student's *t*-test or Wilcoxon rank sum test. The success rate of sedation, the incidence of hypotension, respiratory depression, tachycardia, bradycardia, and paradoxical response will be analyzed using the chi-squared test or Fisher's exact test for categorical variables. A two-sided *P*-value of less than 0.05 will be considered to indicate statistical significance.

Discussion

Remimazolam is a new alternative drug that combines the advantages of traditional sedatives such as midazolam and propofol. Based on this background, applications of this new drug to endoscopic sedation have been attempted in many studies. In regard to diagnostic upper gastrointestinal endoscopy, several randomized controlled phase III trials have been performed to compare the efficacy and safety of remimazolam with propofol [12, 15–17]. A non-inferiority phase III trial in China reported that the success rate of sedation (<1> completion of the whole endoscopy procedure; <2> no requirement for an alternative and/or rescue sedative; <3> administration of up to a maximum of 5 supplemental doses within 15 min after the initial dose) in the remimazolam group was non-inferior to that in the propofol group (97.34% vs. 100.00%). The time to full alertness was significantly shorter in the remimazolam group, and the incidence of hypotension and respiratory depression was significantly lower in the remimazolam group [12]. Another randomized parallel-controlled study reported that the incidence of hemodynamic fluctuations, deep sedation, and adverse reactions was significantly lower in the remimazolam group [15]. One randomized controlled trial attempted the application of remimazolam at different doses (0.2 mg/Kg, 0.3 mg/Kg, and 0.4 mg/Kg) in sedation during upper gastrointestinal endoscopy [16]. In this study, satisfactory efficacy could be obtained with higher concentrations of remimazolam in patients with ASA grade I or II. However, as the dose was progressively increased, the incidence of adverse reactions such as vertigo and prolonged sedation recovery time was also significantly increased. Another randomized controlled trial attempted the combination of remimazolam and propofol [17]. The results of this study revealed that combination therapy had fewer adverse events than propofol monotherapy, a better sedative effect and higher endoscopist satisfaction than remimazolam monotherapy. According to the results of the aforementioned studies, the efficacy of remimazolam seems to be non-inferior to that of propofol, and the safety of remimazolam seems to be superior to that of propofol in diagnostic upper gastrointestinal endoscopy.

As shown in the previous studies [12, 15–17], the rate of adverse events such as hypotension and respiratory depression seems to be considerable in endoscopic sedation using propofol, which might be due to the lack of an antagonist. In practice, midazolam is still used as the main sedative in diagnostic upper and lower gastrointestinal endoscopy in many institutions in Korea due to safety issues and logistical problems. Thus, studies comparing the efficacy and safety of remimazolam and midazolam should provide endoscopists in clinical

practice with helpful information about the appropriate use of benzodiazepines. To date, these studies have been performed in colonoscopy and bronchoscopy [6, 9]. One phase III study evaluating sedation in colonoscopy reported that the success rate of sedation was significantly higher in the remimazolam group [6]. Another prospective randomized controlled trial evaluating sedation in bronchoscopy reported that the time from the end of the procedure to full alertness was significantly shorter in the remimazolam group with favorable safety profiles [9]. However, no phase III trial has compared the efficacy and safety of remimazolam with midazolam in diagnostic upper gastrointestinal endoscopy.

One exploratory phase IIa, randomized study was performed to assess the safety and efficacy of different single doses of remimazolam (0.1 mg/Kg, 0.15 mg/Kg, or 0.2 mg/Kg) and midazolam (0.075 mg/Kg) in upper gastrointestinal endoscopy [18]. The results of this study revealed that a single administration of remimazolam (0.10–0.20 mg/kg) was capable of inducing rapid sedation, with a quick-recovery profile compared with midazolam. Based on these results, we plan to perform this randomized controlled trial to prove the efficacy and safety of remimazolam in diagnostic upper gastrointestinal endoscopy compared with midazolam. We focused on total procedure time (time from the first administration of sedatives to discharge) as an essential component of efficacy. In this trial, we aim to demonstrate the hypothesis that the total procedure time will be shorter using remimazolam than midazolam during diagnostic upper gastrointestinal endoscopy. To the best of our knowledge, this trial is the first randomized controlled study to evaluate both efficacy, focusing on total procedure time and safety in a comparison of remimazolam and midazolam in diagnostic upper gastrointestinal endoscopy. This trial fulfills the need to provide efficacy and safety information on remimazolam in diagnostic upper gastrointestinal endoscopy and should provide endoscopists in clinical practice with helpful information about the appropriate use of benzodiazepines. Based on the results of this trial, a sedation method using remimazolam would be applied preferentially for diagnostic upper gastrointestinal endoscopy in clinical practice. The results of this trial might also provide evidence supporting further trials evaluating the efficacy and safety of remimazolam in various therapeutic endoscopic procedures.

Dissemination policy

Trial results

The collected results of this trial will be presented at scientific conferences at national or international levels and will also be submitted for publication in academic journals that are reviewed by experts in the field.

Authorship

The authors of the present study protocol are Dong-Won Ahn, Jun Kyu Lee, Kwang Hyuk Lee, Taejun Kim, Sun Hyung Kang, Yehyun Park, Sung Bum Kim, and Seong-Jung Kim.

Trial status

Protocol version 1.0 was revised on September 22, 2023. Recruitment began on April 1, 2023, and the approximate date for the completion of recruitment will be January 31, 2024.

Abbreviations

IRB	Institutional Ethics Review Board
ASA	American Society of Anesthesiologists
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MOAA/S	Modified Observer's Assessment of Alertness/Sedation Scale
SD	Standard deviation
SAE	Significant adverse events
CRF	Case report form
DSMB	Data and Safety Monitoring Board
ITT	Intention-to-treat
LOCF	Last observation carried forward

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-026-09712-5.

Additional file 1. Informed consent.

Additional file 2. Participants' compensation protocol.

Additional file 3. SPIRIT checklist.

Acknowledgements
Not applicable.

Provisions for participants compensation
Protocols of participants' compensation to those who suffer harm from trial participation are provided in Additional File 2.

Author's contributions
Ahn DW and Lee JK designed the study protocol and wrote the manuscript. Lee KH designed the study protocol, made critical revisions related to important intellectual content, and approved the manuscript. Kim T, Kang SH, Park Y, Kim SB, and Kim SJ designed the study protocol and contributed to the basis and protocol of endoscopic sedation. All authors contributed to the refinement of this manuscript.

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Data availability
The data generated during the trials, CRFs, and the final dataset can only be accessed by the investigators on the research team.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Ethics Review Board (IRB) of Samsung Medical Center, Sungkyunkwan University School of Medicine (IRB

No. 2022-08-031), and then by the IRB of each institution participating in this study (IRB No. 20–2022-90 in Seoul National University Boramae Medical Center; IRB No. 2022-09-010 in Dongguk University Ilsan Hospital; IRB No. 2022-09-002-001 in Chungnam National University School of Medicine; IRB No. SEUMC 2022-11-013-002 in Ewha Womans University Seoul Hospital; IRB No. 2022-08-059 in Yeungnam University College of Medicine; and IRB No. 2022-11-012-005 in College of Medicine, Chosun University).

Consent for publication
The informed consent form is provided in Additional File 1.

Competing interests
The authors declare that they have no competing interests.

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