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# Remimazolam tosilate combined with flumazenil versus etomidate for procedural sedation in older men undergoing transperineal prostate biopsy: a prospective, participant- and outcome assessor-blinded, randomized controlled superiority trial

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# Title Page

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**Short title:**

Remimazolam Versus Etomidate for Sedation During Prostate Biopsy in Older Patients

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# Abstract

**Background:** Procedural sedation for prostate biopsy in older patients requires effective sedation, cardiorespiratory safety, and rapid recovery. Etomidate provides hemodynamic stability but may cause myoclonus, injection pain, and postoperative nausea and vomiting, and lacks a specific antagonist. Remimazolam has rapid onset and metabolism and can be reversed with flumazenil. We compared remimazolam combined with flumazenil with etomidate in older men undergoing transperineal prostate biopsy.

**Methods:** This single-center, prospective, participant- and outcome assessor-blinded, randomized, parallel-group superiority trial enrolled older male patients undergoing transperineal prostate biopsy. Patients were randomized 1:1 to receive sufentanil-remimazolam followed by flumazenil or sufentanil-etomidate followed by equal-volume saline. The primary outcome was recovery time. Key secondary outcomes were 30-min postoperative change in Digit Symbol Substitution Test

(DSST) score and incidences of hypoxemia, clinically relevant hypotension, and postoperative nausea and vomiting. One interim analysis with O'Brien-Fleming alpha spending was prespecified.

**Results:** Of 136 randomized patients, 130 were included in the interim primary outcome analysis, including 66 in the remimazolam group and 64 in the etomidate group. Recovery time was shorter with remimazolam than with etomidate [1.48 (1.15, 1.90) min vs. 6.61 (5.27, 8.03) min; $P < 0.0001$]. The Hodges-Lehmann median difference was 4.98 min (95% CI, 4.48 to 5.49), exceeding the prespecified superiority margin and meeting the efficacy stopping criterion. The 30-min DSST change did not differ significantly between groups. Hypoxemia was less frequent with remimazolam, although not statistically significant after Holm-Bonferroni adjustment. Postoperative nausea and vomiting was less frequent with remimazolam and remained significant after adjustment. No clinically relevant hypotension, serious adverse events, delayed recovery, or resedation occurred. Myoclonus and injection pain occurred only with etomidate.

**Conclusions:** Remimazolam combined with flumazenil significantly shortened recovery time without evidence of impaired early cognitive recovery in older men undergoing transperineal prostate biopsy. It was also associated with a lower incidence of postoperative nausea and vomiting and no observed increase in clinically relevant hypotension. Larger multicenter studies are warranted to confirm these findings.

**Trial registration:** Chinese Clinical Trial Registry, ChiCTR2400091993. Registered 7 November 2024.

## Keywords

Remimazolam; Flumazenil; Etomidate; Procedural sedation; Recovery time; Prostate biopsy

# Introduction

### Background

Prostate cancer is one of the most common malignancies among men worldwide, and its incidence increases with age. With population aging and the increasing use of prostate-specific antigen screening, the demand for prostate cancer diagnosis continues to rise [1,2]. Prostate biopsy remains an important basis for confirming prostate cancer [3], and the transperineal approach is increasingly used because of its lower infection risk and favorable clinical safety profile [4].

Although transperineal prostate biopsy is usually a short procedure, it remains an invasive diagnostic intervention. In awake patients, ultrasound probe insertion, probe manipulation, and needle puncture may cause pain, anxiety, and stress responses, which can impair cooperation and the patient experience [5]. Older patients often have comorbid hypertension, coronary heart disease, diabetes mellitus, or chronic pulmonary disease, as well as age-related reductions in hepatic and renal function, altered drug distribution and clearance, and increased central nervous system sensitivity. They may therefore be more susceptible to respiratory depression,

hemodynamic fluctuation, delayed recovery, and postoperative cognitive dysfunction during procedural sedation [6,7].

Etomidate has rapid onset and relatively limited hemodynamic effects and is commonly used for anesthetic induction or short procedural sedation in older patients [8]. However, etomidate lacks a specific antagonist, and recovery mainly depends on drug metabolism and clearance. It may also cause adverse effects such as myoclonus, injection pain, postoperative nausea and vomiting, and adrenocortical suppression [8,9].

Remimazolam is an ultra-short-acting benzodiazepine sedative that is rapidly metabolized by tissue esterases and can be reversed with flumazenil. It therefore has potential advantages including rapid onset, rapid recovery, good controllability, and relatively limited respiratory and circulatory effects [10–13].

Most previous studies of remimazolam have focused on comparisons with propofol, whereas direct evidence comparing remimazolam combined with flumazenil versus etomidate in older patients undergoing procedural sedation remains limited [14–19]. For older patients undergoing transperineal prostate biopsy, the sedation strategy that best facilitates rapid recovery while maintaining early cognitive recovery and perioperative safety remains to be clarified.

**Objectives**

This study aimed to compare the recovery benefits and safety risks of remimazolam combined with flumazenil versus etomidate for procedural sedation in older men undergoing transperineal prostate biopsy. The primary objective was to determine whether remimazolam combined with flumazenil significantly shortened recovery

time compared with etomidate. Secondary objectives were to compare early postoperative cognitive recovery, respiratory and circulatory adverse events, postoperative nausea and vomiting, and other drug-related adverse events between the two groups.

# Methods

## Study Design and Ethics

This was a single-center, prospective, randomized, participant- and outcome assessor-blinded, parallel-group superiority trial comparing the efficacy and safety of remimazolam versus etomidate for procedural sedation in older men undergoing transrectal ultrasound-guided transperineal prostate biopsy, with a 1:1 allocation ratio. One interim analysis was prespecified, with group-sequential monitoring and a prespecified efficacy stopping criterion. The study was conducted at The First Affiliated Hospital of Xi'an Jiaotong University, and was approved by the Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University (initial approval No. XJTU1AF2024LSYY-368; amended protocol approval No. XJTU1AF2024LSYY-368-04). The final ethics-approved protocol version used for trial conduct was approved before enrollment of the first participant. This trial is reported in accordance with the CONSORT 2025 statement [20]. The completed CONSORT checklist is provided as an additional file.

## Eligibility Criteria

Older male patients undergoing ultrasound-guided transperineal prostate biopsy at our hospital were enrolled. Inclusion criteria were age ≥ 65 years; body mass index

(BMI) >18 kg/m2 and <30 kg/m2; American Society of Anesthesiologists (ASA) physical status I-III; and ability of the patient and family members to understand the study and provide written informed consent. Exclusion criteria were severe allergy to remimazolam or etomidate; severe pulmonary disease or reduced respiratory reserve, defined as requiring home oxygen therapy, non-invasive ventilation, or exercise tolerance <4 metabolic equivalents; severe hepatic dysfunction, defined as a Child-Turcotte-Pugh score >9; severe renal dysfunction requiring preoperative dialysis; severe cardiac dysfunction, defined as exercise tolerance <4 metabolic equivalents or left ventricular ejection fraction <40%; severe psychiatric disease, cognitive impairment, or inability to complete the Digit Symbol Substitution Test (DSST); and a history of drug or alcohol abuse.

Study procedures and interventions were delivered by qualified clinical personnel. Transperineal prostate biopsy was performed by urologists with appropriate professional qualifications and experience in the procedure. Study drug administration and procedural sedation management were performed by licensed anesthesiologists who had received study protocol training and had experience in anesthesia for urological procedures. Perioperative nursing and monitoring were assisted by registered nurses with anesthesia nursing or operating-room experience.

**Randomization and Allocation Concealment**

Eligible participants who provided informed consent were randomly assigned in a 1:1 ratio to the remimazolam group or the etomidate group. The randomization sequence was generated using SAS 9.4 by an independent statistician who was not involved in

participant recruitment, screening, enrollment, anesthesia implementation, outcome assessment, or data analysis. Variable block randomization was used, with block sizes of 4, 6, or 8. The block sizes and complete randomization sequence were kept only by an independent randomization administrator, and study personnel could not foresee upcoming allocations before participant assignment.

Allocation concealment was implemented using sequentially numbered, opaque, sealed envelopes. The envelopes were kept by the independent randomization administrator and opened sequentially after participant enrollment was completed.

**Blinding**

Participants, primary and secondary outcome assessors, and post-anesthesia care unit (PACU) nurses were blinded to treatment allocation. Because the study drugs required different administration and sedation management, the anesthesiologist administering them was not blinded. This anesthesiologist did not participate in outcome assessment, postoperative follow-up, data verification, or statistical analysis. Statisticians were blinded to treatment allocation, except for the independent statistician responsible for the unblinded interim analysis, whose unblinded results were submitted to the independent data monitoring committee (IDMC). Light-shielding infusion devices and standardized dosing and monitoring procedures were used to support blinding. No emergency unblinding occurred.

**Availability of the Protocol and Statistical Analysis Plan**

The study protocol and statistical analysis plan were developed before trial implementation and were used to guide study design, sample size estimation, interim

analysis, primary and secondary outcome analyses, and safety evaluation. The study protocol and statistical analysis plan are available from the corresponding authors upon reasonable request.

## Patient and Public Involvement

No patients or members of the public were involved in the design, conduct, interpretation, or writing of this study. Before enrollment, all participants received a full explanation of the study objectives, interventions, potential benefits, and risks, and provided written informed consent.

## Protocol Changes and Protocol Deviations

The final ethics-approved protocol version used for trial conduct was approved before enrollment of the first participant. No important changes to eligibility criteria, interventions, or the primary outcome were made after trial commencement. The prespecified primary analysis and interim efficacy stopping rules were retained. An additional post hoc analysis of perioperative blood pressure was conducted, as described in the Statistical Analysis section. Two participants underwent changes in procedure and anesthetic management after randomization, and their primary outcomes could not be assessed as specified in the protocol. These cases are described in the participant flow diagram and the Results section.

## Anesthesia Protocol

After arrival in the procedure room, all participants underwent routine monitoring including electrocardiography, non-invasive blood pressure, peripheral oxygen saturation, and bispectral index monitoring, and intravenous access was established.

All participants received oxygen via nasal cannula at 4 L/min and fasted from solids for 6 h and clear fluids for 2 h before the procedure. The study intervention was administered by the anesthesiologist responsible for procedural sedation management according to the prespecified dosing protocol.

All participants first received slow intravenous sufentanil 0.1 μg/kg. In the remimazolam group, remimazolam 0.2 mg/kg was injected intravenously over 60 s for induction, followed by continuous infusion at 0.4-1.0 mg/kg/h for maintenance. In the etomidate group, etomidate 0.3 mg/kg was administered intravenously for induction, followed by continuous infusion at 0.6-1.2 mg/kg/h for maintenance. The target depth of sedation was a bispectral index of 60-80 with a Ramsay sedation score of 2-4. If sedation was insufficient, the study drug infusion rate could be adjusted according to the prespecified protocol. If adequate sedation could not be achieved at the maximum infusion dose, propofol was used as rescue sedation. Additional sufentanil could be given by the anesthesiologist according to prespecified clinical management principles if inadequate analgesia or body movement occurred during the procedure, and the total dose was recorded.

The study drug was stopped immediately after completion of biopsy. Participants in the remimazolam group received intravenous flumazenil 0.2 mg. If complete recovery did not occur within 60 s, additional flumazenil 0.1 mg was given every minute, up to a maximum total dose of 0.5 mg. Participants in the etomidate group received an equal volume of normal saline at the same time point. After the procedure, participants were transferred to the PACU, where recovery was assessed using the

modified Aldrete score. Discharge from the PACU was permitted when the score was ≥9 and vital signs were stable. Perioperative respiratory support, circulatory management, prevention or rescue treatment for postoperative nausea and vomiting (PONV), and management of other adverse events were implemented according to unified standards and recorded in the case report form.

**Outcomes**

The primary outcome was recovery time, defined as the interval from completion of intravenous flumazenil or placebo injection to the participant's first eye opening, measured in minutes. After study-drug discontinuation and completion of flumazenil or placebo injection, research personnel called the participant's name and instructed the participant to open their eyes every 15 s until eye opening was observed.

Key secondary outcomes were the change in DSST score from preoperative baseline at 30 min postoperatively, the incidence of perioperative hypoxemia, the incidence of perioperative clinically relevant hypotension, and the incidence of PONV. Change in DSST score was defined as the postoperative DSST score at the corresponding time point minus the preoperative baseline DSST score.

Exploratory outcomes included change in DSST score from preoperative baseline at 60 min postoperatively, induction time, procedure duration, PACU stay, total sufentanil dose, Iowa Satisfaction with Anesthesia Scale (ISAS) score, sedation success rate, use of rescue sedatives, total remimazolam or etomidate dose, and incidences of myoclonus, injection pain, resedation, hiccup, and delayed recovery. Induction time was defined as the time interval from initiation of study drug

administration to achievement of the target sedation state, measured in minutes. Procedure duration was defined as the time interval from the start to the end of biopsy, measured in minutes. PACU stay was defined as the time from arrival in the PACU to actual discharge, measured in minutes. Discharge required a modified Aldrete score ≥9 and stable vital signs. Sedation success was defined as completion of the planned procedure without propofol or other rescue sedatives. Definitions and assessment procedures for adverse events are provided below.

**Sample Size**

This study used a superiority design. Because there is no widely accepted minimal clinically important difference for recovery time after procedural sedation in older patients undergoing prostate biopsy, we referred to previous randomized trials using time to eye opening after drug discontinuation as the main recovery outcome and to our pilot data, and considered a 40% relative reduction in recovery time to be a clinically meaningful target effect. In the pilot study, the mean recovery time in the etomidate group was 7.09 min; therefore, a 40% relative reduction corresponded to approximately 2.836 min, which was set as the superiority margin delta. In the pilot study, the mean recovery time in the remimazolam group was 3.13 min, with a between-group mean difference of 3.96 min, suggesting that this effect size was achievable.

The sample size was calculated based on a fixed-sample superiority design, using a one-sided significance level of 0.025, 80% power, and a 1:1 allocation ratio. The calculation showed that 119 evaluable participants were required in each group.

Allowing for an approximately 5% dropout rate or unevaluable primary outcome, the planned total sample size was 252 participants, with 126 participants in each group. O'Brien-Fleming alpha spending was prespecified separately for interim efficacy monitoring to control the overall type I error rate.

**Interim Analysis and Early Stopping Criterion**

One interim analysis and one final analysis were prespecified, with a group-sequential design to control the overall type I error rate. The interim analysis was planned when approximately 50% of the planned information had been accrued and the corresponding participants had completed primary outcome assessment. Because an interim analysis was planned, O'Brien-Fleming alpha spending was used to adjust the significance levels [21]. The overall one-sided significance level was 0.025, with an interim analysis significance level of alpha = 0.0013 and a final analysis significance level of alpha = 0.0245. If the interim analysis showed that the between-group comparison for the primary outcome, recovery time, crossed the prespecified O'Brien-Fleming efficacy monitoring boundary and the Hodges-Lehmann median difference (etomidate minus remimazolam) exceeded the prespecified superiority margin of 2.836 min, the efficacy stopping criterion was considered to have been met. After database freeze, the interim analysis was conducted by an independent statistician according to the prespecified interim analysis plan, and unblinded between-group efficacy and safety results were submitted to the IDMC for review. The IDMC consisted of an anesthesiology expert, a statistician, and an ethics expert who were independent of the study team. The study team, anesthesiologists delivering

sedation, and outcome assessors did not have access to unblinded between-group comparison results before the IDMC issued its recommendation. The IDMC comprehensively evaluated recruitment, data completeness, protocol adherence, interim primary outcome results, adverse events, and serious adverse events, and then provided written recommendations to the principal investigator on whether to continue the trial, modify the protocol, pause recruitment, or terminate the trial early. The principal investigator made subsequent trial management decisions according to the IDMC recommendation, ethical requirements, and study management procedures. The prespecified interim analysis plan and implementation summary are provided as supplementary material.

**Statistical Analysis**

The primary analysis was a complete-case analysis including randomized participants who completed primary outcome assessment. All randomized participants were included in the participant flow and in descriptions of missing primary outcome data. Continuous variables are presented as mean ± standard deviation or median (Q1, Q3), according to distributional characteristics. Categorical variables are presented as counts and percentages. Except for the superiority test of the primary outcome, which was judged using the one-sided significance boundary prespecified in the interim analysis plan, all other statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

According to the prespecified statistical analysis plan, the distribution of recovery time was assessed before between-group comparison. Because recovery time was

skewed, groups were compared using the Wilcoxon rank-sum test, and the Hodges–Lehmann method was used to estimate the location shift and its 95% confidence interval. The effect was expressed as etomidate minus remimazolam; positive values indicated shorter recovery time with remimazolam. The interim stopping criterion was applied as specified in the “Interim Analysis and Early Stopping Criterion” section. For missing primary outcome data, two prespecified sensitivity analyses were performed using conservative percentile imputation and extreme worst-case imputation, both in the direction least favorable to the remimazolam group. In the conservative percentile imputation analysis, missing recovery time values in the remimazolam group were imputed using the 95th percentile of observed values in the etomidate group, and missing recovery time values in the etomidate group were imputed using the 5th percentile of observed values in the remimazolam group. In the extreme worst-case imputation analysis, missing values in the remimazolam group were imputed using the maximum observed value in the etomidate group, and missing values in the etomidate group were imputed using the minimum observed value in the remimazolam group. If the between-group difference remained significant at the interim analysis boundary and the effect estimate still exceeded the prespecified superiority margin in these sensitivity analyses, the primary conclusion was considered robust to missing primary outcome data.

Secondary and exploratory outcomes were analyzed using methods appropriate to variable type and distribution. Continuous variables were compared between groups using the independent-samples t test, Welch t test, or Wilcoxon rank-sum test, as

appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test, and risk differences, relative risks, and 95% confidence intervals were reported as appropriate. The four prespecified key secondary outcomes were adjusted for multiple comparisons using the Holm-Bonferroni method [22]. For DSST, scores measured before anesthesia and at 30 and 60 min after recovery were analyzed using a prespecified linear mixed-effects model. Recovery was defined as the participant's first eye opening following completion of flumazenil or placebo injection. Fixed effects were treatment group, categorical time (baseline, 30 min after recovery, and 60 min after recovery), and the group-by-time interaction. The model was fitted by restricted maximum likelihood using an unstructured covariance matrix for repeated measurements within participants; no participant-specific random effect was specified. Baseline DSST was treated as a repeated outcome rather than as a covariate. Missing DSST measurements were not imputed; all available measurements from the 136 randomized participants, including participants with baseline measurements only, contributed to the likelihood-based analysis under a missing-at-random assumption. For PACU stay, complete-case analyses used observed data only. Consistent with the protocol-specified approach for continuous exploratory outcomes with substantial missingness, a multiple-imputation sensitivity analysis was conducted in all 136 randomized participants. PACU stay was log-transformed before imputation. Under a missing-at-random assumption conditional on randomized group, age, body mass index, ASA physical status (III vs II), and baseline DSST score, 20 imputed data sets were generated by fully conditional specification using predictive mean matching

with five donors and 20 iterations. Each completed data set was analyzed using linear regression of log PACU stay on randomized group, and estimates and standard errors were combined using Rubin's rules. Exponentiated pooled coefficients are reported as geometric mean ratios for remimazolam versus etomidate, with nominal two-sided 95% confidence intervals. For the two participants who underwent a changed procedure and anesthetic regimen, imputed values represent hypothetical PACU stay under the originally planned procedure and randomized treatment strategy rather than under the altered regimen. A prespecified supportive adjusted analysis of recovery time was performed in the complete-case primary analysis population using a generalized linear model with a gamma distribution and log link. The model included procedure duration, age, ASA physical status, BMI, serum creatinine, alanine aminotransferase, history of hypertension, history of diabetes mellitus, and history of coronary heart disease. Exponentiated regression coefficients are presented as adjusted mean ratios with nominal Wald 95% confidence intervals. No subgroup analyses were performed. An additional post hoc analysis of perioperative SBP, DBP, and MAP was conducted to describe blood pressure patterns, as no clinically relevant hypotension was recorded among participants with available safety data. This analysis was exploratory and did not replace the prespecified analysis of clinically relevant hypotension. Separate linear mixed-effects models were fitted for each variable. Fixed effects were treatment group, categorical time (before anesthesia, after induction, at the start of biopsy, 3 min after biopsy start, and before leaving the procedure room), and the group-by-time interaction. Models were fitted by restricted maximum likelihood using an

unstructured covariance matrix for repeated measurements within participants; no participant-specific random effect was specified. Kenward-Roger degrees of freedom were used. Missing hemodynamic measurements were not imputed, and each model used all available observations for the corresponding variable under a missing-at-random assumption. Least-squares means with nominal 95% confidence intervals were estimated for each group-by-time combination. Statistical analyses were performed using SAS 9.4.

**Safety and Adverse Event Assessment**

Adverse events were recorded by blinded data collectors from anesthetic induction to PACU discharge. Safety assessments covered hypoxemia, clinically relevant hypotension, PONV, myoclonus, injection pain, resedation, hiccup, delayed recovery, serious adverse events, and other adverse events.

Hypoxemia was defined as SpO2 <93% lasting at least 30 s, or a need to increase oxygen flow, perform jaw thrust, insert an oropharyngeal airway, or provide another airway intervention because of decreased oxygenation. Clinically relevant hypotension was defined as systolic blood pressure (SBP) <90 mmHg, a decrease in SBP of more than 30% from baseline, or mean arterial pressure (MAP) <60 mmHg. PONV was defined as nausea, retching, or vomiting during postoperative observation; rescue antiemetic use was also recorded. Myoclonus was defined as involuntary muscle or limb jerks after study-drug administration. Injection pain was defined as participant-reported pain or injection-related limb withdrawal, grimacing, or groaning during injection. Hiccup was defined as paroxysmal involuntary diaphragmatic

contraction, with or without a characteristic inspiratory sound, during perioperative observation. Resedation was defined as a decrease of at least 1 point in the Richmond Agitation-Sedation Scale score after initial recovery during PACU observation. Delayed recovery was defined as delayed awakening after study-drug discontinuation and completion of flumazenil or placebo injection that, in the investigator's judgment, required additional observation or management.

Serious adverse events were defined as events resulting in death, life-threatening events, hospitalization or prolonged hospitalization, permanent injury, or events requiring important medical intervention. For each adverse event, the time of occurrence, management, outcome, and possible relationship to the study drug were recorded.

# Results

### Participant Flow and Baseline Characteristics

A total of 152 older men scheduled for transperineal prostate biopsy were assessed for eligibility. Of these, 10 did not meet the inclusion criteria and 6 declined to participate. The remaining 136 participants were randomized to the remimazolam or etomidate group, with 68 in each group. All participants received their assigned study medication.

Primary outcome data were missing for two participants in the remimazolam group and four in the etomidate group. In the remimazolam group, one participant declined assessment and one underwent a change in surgical approach. In the etomidate group, two participants declined assessment, one underwent a change in surgical approach,

and one had data lost because of a system failure. The complete-case interim primary outcome analysis included 66 participants in the remimazolam group and 64 in the etomidate group, with an overall missing data rate of 4.41% (6/136). Safety data were available for the three participants who declined primary outcome assessment, giving safety analysis populations of 67 and 66 participants, respectively. Participant flow is shown in Figure 1.

Recruitment began on June 6, 2025. The last participant included in the interim primary outcome analysis completed primary outcome assessment on December 28, 2025. The interim analysis met the prespecified efficacy stopping criterion, and recruitment was stopped on January 1, 2026, following the IDMC's recommendation. Baseline characteristics of all 136 randomized participants are presented in Table 1, including demographic characteristics, ASA physical status, comorbidities, hepatic and renal function indices, and preoperative DSST scores.

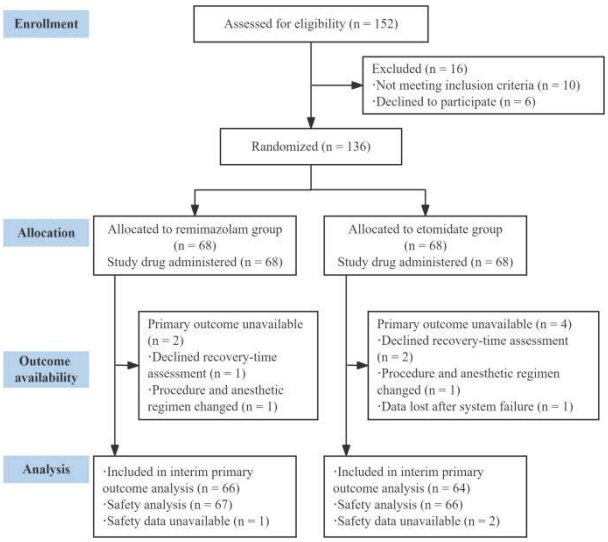



**Fig. 1 Participant flow diagram**

Of 152 patients assessed for eligibility, 136 were randomized, with 68 assigned to each group.

The interim primary outcome analysis included 66 participants in the remimazolam group and 64 in the etomidate group; safety analyses included 67 and 66 participants, respectively. Participants with missing primary outcome data contributed to other analyses when relevant data were available. Recruitment was stopped following the IDMC recommendation after the prespecified interim efficacy stopping criterion was met. IDMC, independent data monitoring committee.

**Table 1 Baseline characteristics of participants**

| Characteristic | Remimazolam group (n = 68) | Etomidate group (n = 68) |
|---|---|---|
| Age, years | 70 (67, 74) | 70 (67, 73) |
| Height, cm | 170 (167, 173) | 170 (165, 174) |
| Weight, kg | 67.74 ± 8.19 | 68.42 ± 9.87 |
| BMI, kg/m² | 23.40 ± 2.63 | 23.74 ± 2.71 |
| ASA physical status II | 60 (88.24%) | 63 (92.65%) |
| ASA physical status III | 8 (11.76%) | 5 (7.35%) |
| Hypertension | 29 (42.65%) | 30 (44.12%) |
| Diabetes mellitus | 18 (26.47%) | 12 (17.65%) |
| Coronary heart disease | 5 (7.35%) | 2 (2.94%) |
| AST, U/L | 21.0 (18.0, 25.0) | 21.5 (17.0, 25.5) |
| ALT, U/L | 18.0 (14.0, 25.0) | 18.0 (13.0, 24.0) |
| Total bilirubin, μmol/L | 16.00 (12.15, 19.45) | 15.45 (12.15, 19.30) |

| | | |
|---|---|---|
| Albumin, g/L | 43.53 ± 2.96 | 43.61 ± 2.85 |
| Blood urea nitrogen, mmol/L | 6.39 ± 1.65 | 6.53 ± 1.49 |
| Serum creatinine, μmol/L | 66.5 (61.5, 73.5) | 72.0 (61, 77.5) |
| Baseline DSST score | 32.01 ± 10.31 | 30.15 ± 10.20 |

Data are presented as mean ± SD, median (Q1, Q3), or n (%). SD, standard deviation; Q1, first quartile; Q3, third quartile; ASA, American Society of Anesthesiologists; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; DSST, Digit Symbol Substitution Test.

## Primary Outcome

Recovery time was skewed. The complete-case analysis showed that recovery time was significantly shorter in the remimazolam group than in the etomidate group [1.48 (1.15, 1.90) min vs. 6.61 (5.27, 8.03) min, $P < 0.0001$; Table 2 and Figure 2]. Calculated as etomidate minus remimazolam, the Hodges-Lehmann median difference was 4.975 min, exceeding the prespecified superiority margin of 2.836 min and meeting the O'Brien-Fleming-adjusted interim analysis significance boundary (alpha = 0.0013). Conservative percentile imputation and extreme worst-case imputation sensitivity analyses both showed that the between-group difference remained statistically significant (both $P < 0.0001$), and the Hodges-Lehmann median difference was 4.740 min in both analyses, still exceeding the prespecified superiority margin. These findings indicated that the primary conclusion was robust to missing primary outcome data (Table 2). The interim analysis did not identify adverse safety signals triggering prespecified safety stopping rules, and the IDMC recommended

early trial termination because the prespecified efficacy stopping criterion had been met.

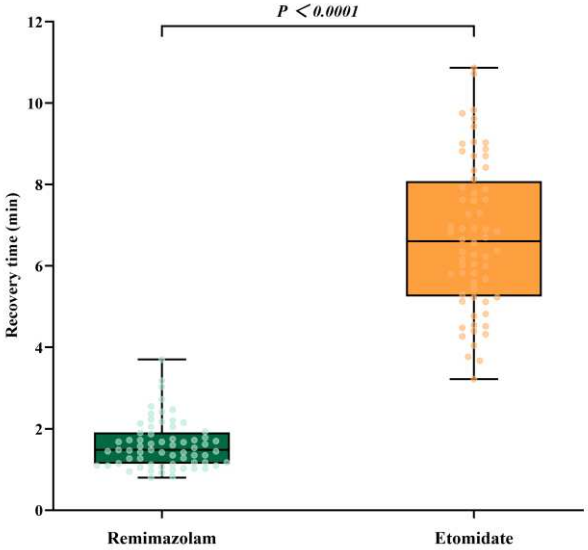



**Fig. 2 Distribution of recovery time by treatment group**

Boxes indicate the median and interquartile range, whiskers indicate the minimum and maximum values, and dots indicate individual participants. Recovery time was significantly shorter in the remimazolam group than in the etomidate group (Hodges-Lehmann median difference, 4.975 min; Wilcoxon rank-sum test, P < 0.0001).

**Table 2 Primary outcome and sensitivity analyses**

| Analysis | Remimazolam group | Etomidate group | Hodges-Lehmann difference (E - R), min (95% CI) | P value | Superiority margin met |
|---|---|---|---|---|---|
| Complete-case analysis | 1.48 (1.15, 1.90), n = 66 | 6.61 (5.27, 8.03), n = 64 | 4.98 (4.48 to 5.49) | < 0.0001 | Yes |
| Conservative percentile imputation | 1.51 (1.16, 1.99), n = 68 | 6.36 (5.13, 7.91), n = 68 | 4.74 (4.20 to 5.25) | < 0.0001 | Yes |
| Extreme worst-case imputation | 1.51 (1.16, 1.99), n = 68 | 6.36 (5.13, 7.91), n = 68 | 4.74 (4.20 to 5.25) | < 0.0001 | Yes |

Data are presented as median (Q1, Q3). E − R indicates etomidate minus remimazolam; positive values

indicate a shorter recovery time in the remimazolam group. P values were calculated using the Wilcoxon rank-sum test. The prespecified superiority margin was 2.836 min. Conservative percentile imputation and extreme worst-case imputation were performed for missing primary outcome data as sensitivity analyses. In both sensitivity analyses, missing values were imputed in the direction least favorable to the remimazolam group.

## Key Secondary Outcomes

The change in DSST score at 30 min postoperatively did not differ significantly between groups (Table 3). Repeated-measures mixed-effects modeling showed a significant time effect ($P < 0.0001$). DSST scores decreased at 30 min and returned to near or slightly above baseline at 60 min postoperatively. Neither the treatment group effect nor the group-by-time interaction was statistically significant, providing no evidence of a between-group difference in early postoperative DSST trajectories (Figure 3).

Safety data were available for 67 participants in the remimazolam group and 66 in the etomidate group; data were unavailable for one and two participants, respectively. Adverse events and safety outcomes are summarized in Table 4, with selected events shown in Figure 4. PONV occurred less frequently in the remimazolam group than in the etomidate group [4/67 (6.0%) vs. 14/66 (21.2%); raw $P = 0.0102$], and the difference remained statistically significant after Holm–Bonferroni adjustment (adjusted $P = 0.0408$). Hypoxemia was also less frequent in the remimazolam group [5/67 (7.5%) vs. 14/66 (21.2%); raw $P = 0.0235$], but the difference was not statistically significant after adjustment for the four prespecified key secondary

outcomes (adjusted P = 0.0704). No clinically relevant hypotension, apparent bradycardia, apparent tachycardia, serious adverse events, delayed recovery, or resedation was recorded among participants with available safety data.

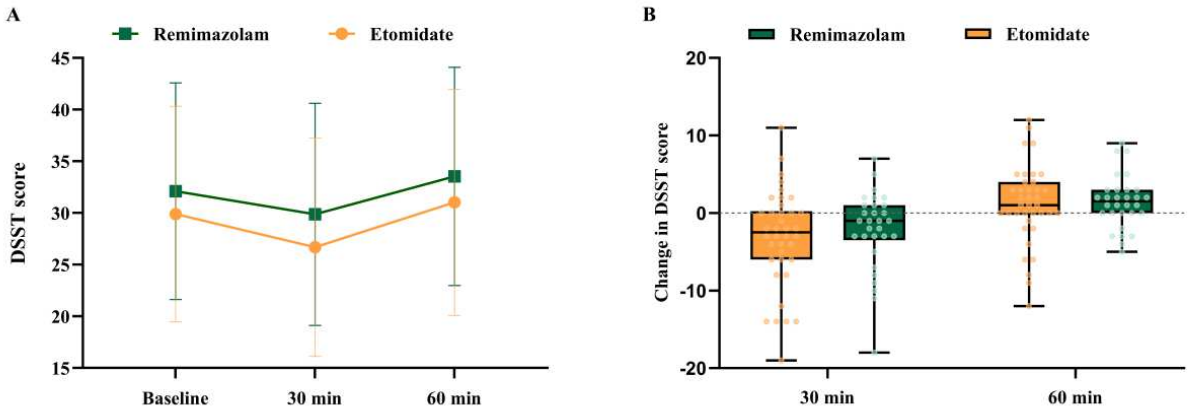



**Fig. 3 Postoperative cognitive recovery assessed by DSST**

(A) DSST scores at baseline, 30 min, and 60 min after the procedure. Points indicate mean DSST scores, and error bars indicate standard deviations. (B) Changes from baseline in DSST scores at 30 min and 60 min after the procedure. Boxes indicate the median and interquartile range, whiskers indicate the minimum and maximum values, and dots indicate individual participants. Change in DSST score was calculated as postoperative DSST score minus baseline DSST score. DSST, Digit Symbol Substitution Test.

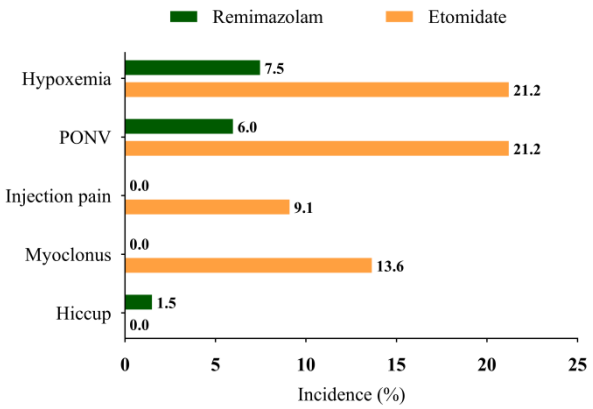



**Fig. 4 Adverse events and safety outcomes**

Bars indicate the percentage of participants with each adverse event. Outcomes with no events in either group are reported in Table 4 but omitted from the figure. PONV, postoperative nausea and vomiting.

**Table 3 Postoperative cognitive recovery assessed by DSST**

| Outcome | Remimazolam group | Etomidate group | Between-group estimate (95% CI) | Raw P value | Holm-adjusted P value |
|---|---|---|---|---|---|
| Baseline DSST score | 32.01 ± 10.31 (n = 68) | 30.15 ± 10.2 (n = 68) | NA | NA | NA |
| 30-min DSST score | 29.88 ± 10.71 | 26.77 ± 10.41 | NA | NA | NA |
| 60-min DSST score | 33.53 ± 10.54 | 31.05 ± 10.93 | NA | NA | NA |
| Change from baseline at 30 min | -1.00 (-3.00, 1.00) | -2.50 (-6.00, 0.00) | 1.00 (0.00 to 3.00) | 0.152 | 0.305 |
| Change from baseline at 60 min | 1.50 (0.00, 3.00) | 1.00 (-1.00, 3.00) | 0.00 (-1.00 to 1.00) | 0.597 | NA |

Baseline DSST scores were available for all 136 randomized participants (68 per group). Postoperative scores and changes from baseline were available for 66 participants in the remimazolam group and 64 in the etomidate group. Data are presented as mean ± SD or median (Q1, Q3). Change from baseline was calculated as postoperative minus baseline DSST score. Between-group effects on change scores are Hodges–Lehmann location-shift estimates (remimazolam minus etomidate), with 95% confidence intervals; positive values indicate a greater increase or smaller decrease in the remimazolam group. Raw P values were obtained using the two-sided Wilcoxon rank-sum test with a normal approximation and continuity correction. The 30-min change was included in the Holm–Bonferroni adjustment for the four prespecified key secondary outcomes; the 60-min change was exploratory and unadjusted. The repeated-measures model used available scores from all 136 randomized participants, including six with baseline scores only. The time effect was significant ($P < 0.0001$), whereas the group effect ($P = 0.152$) and group-by-time interaction ($P = 0.778$) were not. DSST, Digit Symbol Substitution Test; SD,

standard deviation; CI, confidence interval; NA, not applicable.

**Table 4 Adverse events and safety outcomes**

| Outcome | Remimazolam group (n = 67) | Etomidate group (n = 66) | Risk difference (R − E), % | Relative risk (R / E) | Raw P value | Holm-adjusted P value |
|---|---|---|---|---|---|---|
| Hypoxemia | 5/67 (7.5%) | 14/66 (21.2%) | −13.7 (−25.8 to −1.7) | 0.35 (0.14 to 0.88) | 0.0235 | 0.0704 |
| PONV | 4/67 (6.0%) | 14/66 (21.2%) | −15.2 (−27.1 to −3.5) | 0.28 (0.10 to 0.77) | 0.0102 | 0.0408 |
| Clinically relevant hypotension | 0/67 (0.0%) | 0/66 (0.0%) | 0.0 (-5.5 to 5.4) | Not estimable | NA | 1.0000 |
| Injection pain | 0/67 (0.0%) | 6/66 (9.1%) | -9.1 (-18.4 to -1.8) | 0.00 (0.00 to 0.61) | 0.0133 | Not applicable |
| Serious adverse events | 0/67 (0.0%) | 0/66 (0.0%) | 0.0 (-5.5 to 5.4) | Not estimable | NA | Not applicable |
| Myoclonus | 0/67 (0.0%) | 9/66 (13.6%) | −13.6 (−23.9 to −5.3) | 0.00 (0.00 to 0.41) | 0.0014 | Not applicable |
| Hiccup | 1/67 (1.5%) | 0/66 (0.0%) | 1.5 (−4.1 to 8.0) | ∞ (0.26 to ∞) | 1.0000 | Not applicable |
| Delayed recovery | 0/67 (0.0%) | 0/66 (0.0%) | 0.0 (-5.5 to 5.4) | Not estimable | NA | Not applicable |
| Resedation | 0/67 (0.0%) | 0/66 (0.0%) | 0.0 (-5.5 to 5.4) | Not estimable | NA | Not applicable |

Data are presented as n/N (%), where N is the number of participants with available safety data. Of 68 participants randomized per group, safety data were missing for one in the remimazolam group and two in the etomidate group; missing outcomes were not imputed or counted as non-events. Risk differences (R − E) are expressed in percentage points with Newcombe 95% confidence intervals (CIs); negative values favor remimazolam. Relative risks (R/E) are presented with score-based 95% CIs. ∞ indicates events in the remimazolam group but none in the etomidate group; relative risks are not estimable

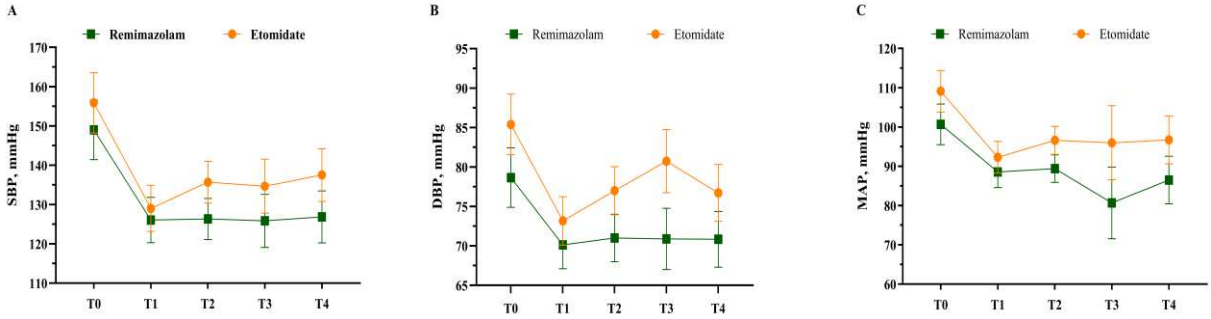
when both groups have zero events. Two-sided P values were calculated using Pearson's chi-square test or Fisher's exact test when any expected cell count was <5; raw P values are NA when both groups have zero events. Holm–Bonferroni adjustment included four prespecified key secondary outcomes: 30-min change in DSST score (Table 3; raw P = 0.1523), hypoxemia, PONV, and clinically relevant hypotension. Hypotension was retained in this family with P = 1.0000. Adjusted P values outside this family are marked "Not applicable." R, remimazolam; E, etomidate; DSST, Digit Symbol Substitution Test; NA, not applicable; PONV, postoperative nausea and vomiting.

## Exploratory Outcomes and Other Safety Observations

Exploratory outcomes are shown in Table 5. Among participants with available intraoperative data, successful sedation without rescue medication was achieved in 67/67 participants in the remimazolam group and 66/66 in the etomidate group. Induction time, procedure duration, and sufentanil dose were similar between groups. PACU stay was shorter in the remimazolam group in the observed-data analysis, and the supplementary multiple-imputation analysis also indicated a shorter stay. ISAS scores were higher in the remimazolam group (P = 0.036). These exploratory comparisons were not adjusted for multiplicity.

Regarding other adverse events, myoclonus and injection pain did not occur in the remimazolam group, whereas 9 cases of myoclonus and 6 cases of injection pain occurred in the etomidate group. One case of hiccup occurred in the remimazolam group, and no hiccup occurred in the etomidate group. Hypoxemia events in both groups resolved after increasing oxygen flow, jaw thrust, or insertion of an

545 oropharyngeal airway, and no participant required placement of a supraglottic airway
546 device or tracheal intubation (Table 4 and Figure 4).
547 Post hoc linear mixed-effects modeling showed that perioperative SBP, DBP, and
548 MAP changed over time in both groups, but the group-by-time interactions were not
549 statistically significant, suggesting generally similar perioperative blood pressure
550 trends between groups (Table 6 and Figure 5).



551

552 **Fig. 5 Perioperative blood pressure changes**

553 Data are shown as least-squares means with 95% confidence intervals estimated from post hoc linear
554 mixed-effects models. A, systolic blood pressure; B, diastolic blood pressure; C, mean arterial pressure.
555 T0, before anesthesia; T1, after induction; T2, start of biopsy; T3, 3 min after biopsy start; T4, before
556 leaving the procedure room. Missing measurements were not imputed, and all available observations
557 were included in the models. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean
558 arterial pressure; CI, confidence interval.

559 **Table 5 Exploratory outcomes**

| Outcome | Remimazolam group | Etomidate group | Effect estimate (95% CI) | P value |
|---|---|---|---|---|
| Induction time, min | 0.95 (0.87, 1.07) | 0.93 (0.78, 1.02) | 0.05 (0.00 to 0.12) | 0.072 |

| | | | | |
|---|---|---|---|---|
| Procedure duration, min | 11.67 ± 3.56 | 11.88 ± 3.72 | −0.20 (−1.45 to 1.05) | 0.756 |
| PACU stay, min | 34.15 (22.20, 35.25) | 38.35 (32.70, 44.45) | −9.40 (−10.50 to −1.00) | 0.034 |
| Sufentanil dose, μg | 6.9 (6.5, 7.5) | 6.9 (6.15, 8.0) | −0.10 (−0.50 to 0.20) | 0.512 |
| ISAS score | 2.27 (1.63, 2.55) | 1.91 (0.77, 2.50) | 0.27 (0.00 to 0.64) | 0.036 |
| Successful sedation without rescue medication | 67/67 (100%) | 66/66 (100%) | Not estimable | NA |
| Remimazolam dose, mg | 30 (26, 34) | NA | Not estimated | NA |
| Etomidate dose, mg | NA | 36 (31, 40) | Not estimated | NA |

Data are presented as mean ± SD, median (Q1, Q3), or n/N (%), as appropriate. Intraoperative outcomes and study-drug doses were available for 67 participants in the remimazolam group and 66 in the etomidate group; ISAS scores were available for 66 and 64 participants, respectively. Effect estimates shown in the table are mean differences or Hodges–Lehmann location-shift estimates (remimazolam minus etomidate), with 95% confidence intervals. P values are exploratory and were not adjusted for multiple comparisons. PACU stay results are based on 52 observed cases per group. A supplementary analysis using 20 multiple imputations included all 136 randomized participants, with PACU stay missing for 16 of 68 participants in each group, and also indicated a shorter PACU stay with remimazolam (geometric mean ratio [remimazolam/etomidate], 0.78; 95% CI, 0.72 to 0.86; P < 0.0001). For the two participants whose procedure or anesthetic regimen changed, imputation assumed continuation of the original procedure and assigned treatment. Study-drug doses were summarized within each group without between-group comparison because different sedatives were used. Successful sedation without rescue medication was defined as completion of the procedure without rescue sedative medication. SD, standard deviation; ISAS, Iowa Satisfaction with Anesthesia Scale;

574 PACU, post-anesthesia care unit; CI, confidence interval; NA, not applicable.

575 **Table 6 Perioperative blood pressure changes**

| Variable | Group | T0 | T1 | T2 | T3 | T4 | P for time | P for group × time |
|---|---|---|---|---|---|---|---|---|
| SBP, mmHg | Remimazolam | 149 (141, 157) | 126 (120, 132) | 126 (121, 132) | 126 (119, 133) | 127 (120, 133) | < 0.05 | 0.095 |
| | Etomidate | 156 (148, 164) | 129 (123, 135) | 136 (130, 141) | 135 (128, 142) | 138 (131, 144) | | |
| DBP, mmHg | Remimazolam | 79 (75, 82), n = 62 | 70 (67, 73) | 71 (68, 74) | 71 (67, 75) | 71 (67, 74) | < 0.05 | 0.067 |
| | Etomidate | 85 (82, 89), n = 60 | 73 (70, 76) | 77 (74, 80) | 81 (77, 85), n = 60 | 77 (73, 80) | | |
| MAP, mmHg | Remimazolam | 101 (95, 106) | 89 (85, 93) | 89 (86, 93) | 81 (72, 90), n = 58 | 86 (80, 93) | < 0.05 | 0.096 |
| | Etomidate | 109 (104, 114) | 92 (88, 96) | 97 (93, 100) | 96 (87, 105), n = 52 | 97 (91, 103) | | |

576 Data are presented as least-squares means (95% CIs) estimated from post hoc linear mixed-effects
577 models. Unless otherwise indicated, observed measurements were available for 66 participants in the
578 remimazolam group and 64 in the etomidate group at each time point. Sample sizes are specified where
579 fewer measurements were available. Missing measurements were not imputed; models used all
580 available observations. T0, before anesthesia; T1, after induction; T2, start of biopsy; T3, 3 min after
581 biopsy start; T4, before leaving the procedure room. SBP, systolic blood pressure; DBP, diastolic blood
582 pressure; MAP, mean arterial pressure; CI, confidence interval.

583 **Multivariable Analysis**

584 The multivariable analysis results are shown in Table 7. The gamma generalized
585 linear model showed that, after adjustment for procedure duration, age, ASA physical

status, BMI, serum creatinine, alanine aminotransferase, history of hypertension, history of diabetes mellitus, and history of coronary heart disease, treatment group remained significantly associated with recovery time (beta = -1.422, P < 0.0001). The adjusted mean ratio was 0.241 (95% CI, 0.218-0.267), indicating that recovery time in the remimazolam group was approximately 24.1% of that in the etomidate group. Procedure duration was also positively associated with recovery time (beta = 0.034, P < 0.0001), whereas the other covariates showed no significant independent associations.

**Table 7 Multivariable gamma generalized linear model for recovery time**

| Variable | β | SE | Adjusted mean ratio | 95% CI | P value |
|---|---|---|---|---|---|
| Remimazolam vs etomidate | -1.4219 | 0.0513 | 0.241 | 0.218 to 0.267 | ＜0.0001 |
| Procedure duration, min | 0.0335 | 0.0070 | 1.034 | 1.020 to 1.048 | ＜0.0001 |
| Age, years | -0.0077 | 0.0064 | 0.992 | 0.980 to 1.005 | 0.2295 |
| ASA physical status III vs II | -0.0631 | 0.1085 | 0.939 | 0.759 to 1.161 | 0.5610 |
| BMI, $kg/m^2$ | 0.0071 | 0.0100 | 1.007 | 0.987 to 1.027 | 0.4806 |
| ALT, U/L | 0.0010 | 0.0019 | 1.001 | 0.997 to 1.005 | 0.5820 |
| Serum creatinine, μmol/L | -0.0001 | 0.0019 | 1.000 | 0.996 to 1.004 | 0.9660 |
| Hypertension | -0.0732 | 0.0558 | 0.929 | 0.833 to 1.037 | 0.1899 |
| Diabetes mellitus | 0.0711 | 0.0681 | 1.074 | 0.940 to 1.227 | 0.2962 |
| Coronary heart disease | 0.0523 | 0.1166 | 1.054 | 0.838 to 1.324 | 0.6539 |

A supportive adjusted analysis was performed using a gamma generalized linear model with a log link

596 in 130 participants with observed recovery times and complete covariate data (66 in the remimazolam
597 group and 64 in the etomidate group). Missing recovery times were not imputed for this analysis.
598 Adjusted mean ratios were calculated as exp(β), with 95% CIs obtained by exponentiating the Wald
599 confidence limits for β. Etomidate, ASA physical status II, and absence of each comorbidity were the
600 reference categories. Ratios for continuous covariates represent a one-unit increase in the stated units. P
601 values are from Wald tests. ASA, American Society of Anesthesiologists; BMI, body mass index; ALT,
602 alanine aminotransferase; CI, confidence interval; SE, standard error.

# 603 Discussion

604 In this single-center randomized trial of older men undergoing transperineal prostate
605 biopsy, remimazolam tosilate combined with flumazenil shortened recovery time
606 compared with etomidate. This faster recovery was not accompanied by an observed
607 worsening of early cognitive recovery or an increased risk of clinically relevant
608 hemodynamic instability. The remimazolam group also had fewer cases of
609 postoperative nausea and vomiting, and no myoclonus or injection pain was observed.
610 Because the trial was stopped early for efficacy at a prespecified interim analysis,
611 these findings should be interpreted with appropriate caution and confirmed in larger
612 multicenter studies.

613 Transperineal prostate biopsy is usually a short ambulatory or day-case procedure, in
614 which rapid recovery, procedural comfort, and early discharge readiness are clinically
615 relevant. Etomidate remains useful because of its rapid onset and relative
616 cardiovascular stability, but it has no specific antagonist and is associated with
617 adverse effects such as myoclonus, injection pain, and postoperative nausea and

618 vomiting [8,9]. Remimazolam is an ultra-short-acting benzodiazepine that is rapidly
619 hydrolyzed by tissue esterases and can be antagonized by flumazenil [10-13]. These
620 properties make it an attractive option for short procedural sedation, particularly when
621 predictable recovery is important.
622 Median recovery time was 1.48 min in the remimazolam group and 6.61 min in the
623 etomidate group, and the Hodges-Lehmann median shift exceeded the prespecified
624 superiority margin. The result was maintained in conservative sensitivity analyses for
625 missing primary outcome data. A reduction of about 5 min may appear modest, but in
626 a short outpatient procedure it may allow earlier communication, assessment, and
627 transfer through the PACU pathway. Similar recovery advantages after flumazenil
628 reversal have been reported in studies comparing remimazolam-based anesthesia with
629 propofol-based regimens [14-16].
630 Faster eye opening did not appear to come at the expense of early cognitive recovery.
631 DSST scores decreased at 30 min after the procedure and returned close to, or slightly
632 above, baseline at 60 min in both groups. The repeated-measures analysis showed a
633 clear time effect, but neither the group effect nor the group-by-time interaction was
634 statistically significant. These findings suggest that the rapid clinical recovery seen
635 with remimazolam and flumazenil was not associated with a detectable decline in
636 early psychomotor recovery in this study. This is relevant in older patients, because
637 eye opening alone does not necessarily mean that attention, psychomotor speed, and
638 executive function have recovered.
639 Postoperative nausea and vomiting occurred less often in the remimazolam group, and

this difference remained statistically significant after Holm-Bonferroni adjustment. Although PONV is rarely life-threatening, it can delay discharge, reduce patient satisfaction, and increase the need for rescue medication. Etomidate-related nausea and vomiting have been reported in previous sedation and anesthesia studies [8,18,19]. In the present study, sufentanil dose was similar between groups, so differences in opioid exposure are unlikely to fully explain the difference in PONV.

Hypoxemia remains a concern during procedural sedation in older patients. A prospective study of gastrointestinal endoscopy identified older age, higher BMI, and habitual snoring as factors associated with hypoxemia [23]. In our study, hypoxemia occurred less frequently with remimazolam than with etomidate (7.5% vs. 21.2%), but the difference was not statistically significant after Holm-Bonferroni adjustment (adjusted P = 0.0704). The observed difference warrants further investigation but does not establish a respiratory safety advantage. Hypoxemic episodes were managed with supplemental oxygen adjustment and airway interventions, including an oropharyngeal airway when needed. No participant required a supraglottic airway device or tracheal intubation.

Hemodynamic stability is an important concern in older patients undergoing procedural sedation. No clinically relevant hypotension occurred in either group. In post hoc linear mixed-effects models, systolic blood pressure, diastolic blood pressure, and mean arterial pressure changed over time, but the group-by-time interactions were not statistically significant. These findings suggest broadly similar perioperative blood pressure trends between groups. However, because these analyses were post hoc and

some measurements were missing at selected time points, they should be regarded as descriptive and supportive. Previous trials have also suggested that remimazolam can provide stable hemodynamics in different procedural and anesthetic settings [17-19].

Myoclonus and injection pain were observed in the etomidate group but not in the remimazolam group. These events are well recognized with etomidate and may affect comfort during induction and procedural stability [8,9]. All patients in this trial received sufentanil before sedative administration, which may have reduced the frequency or severity of etomidate-related myoclonus. These findings are consistent with the known adverse-effect profile of etomidate, but the comparisons were exploratory and were not adjusted for multiplicity.

One patient in the remimazolam group developed hiccup. The episode was transient, resolved spontaneously, and did not interrupt the procedure. Hiccup has been described after remimazolam administration and is usually self-limited [24,25]. Nevertheless, procedural sedation is performed without a protected airway, so hiccup should not be dismissed entirely, especially in patients with reflux or aspiration risk.

No resedation occurred after flumazenil reversal in this trial. This may be related to the short procedure duration, limited cumulative remimazolam exposure, exclusion of patients with severe hepatic or renal dysfunction, and the use of titrated flumazenil reversal followed by monitoring. However, delayed or recurrent sedation after remimazolam reversal has been reported [26,27]. Continued observation after flumazenil administration therefore remains prudent, particularly in older patients and in those with possible delayed drug clearance.

Other exploratory outcomes should be read in context. Both regimens achieved successful sedation without rescue medication, and induction time and sufentanil dose were similar between groups. These findings suggest that both regimens provided adequate sedation under the conditions of this trial. The shorter PACU stay and higher satisfaction score in the remimazolam group may be clinically relevant, but these outcomes were not powered for confirmatory testing and were not adjusted for multiplicity. They should therefore be considered hypothesis-generating.

This study has several strengths. It focused on a common short procedural sedation setting in older patients, used a randomized parallel-group superiority design, and included blinded outcome assessment. It also evaluated several domains relevant to recovery after procedural sedation, including recovery time, early cognitive function, respiratory events, blood pressure changes, PONV, and drug-related adverse events. The prespecified interim analysis, conservative sensitivity analyses for missing primary outcome data, and multiplicity adjustment for key secondary outcomes further support the internal validity of the main findings.

# Limitations

This study has several limitations. First, it was conducted at a single center, and anesthesia workflow, patient management, and operator experience may affect the results; therefore, generalization to other institutions should be cautious. Second, the study population was limited to older men undergoing transperineal prostate biopsy, and the results cannot be directly extrapolated to women, younger patients, critically ill patients, or other surgical procedures. Third, enrollment was stopped after the

prespecified interim analysis met the efficacy stopping criterion. Although this was consistent with the study protocol and ethical requirements, randomized trials stopped early for benefit may overestimate treatment effects, and the final sample size was smaller than planned, reducing power to detect rare adverse events and differences in some secondary outcomes. Fourth, the observation period was short and focused mainly on PACU and early postoperative recovery; longer-term cognitive function, quality of life, and delayed adverse events were not assessed. Fifth, myoclonus, injection pain, hiccup, patient satisfaction, and PACU stay were exploratory outcomes, and these findings should be interpreted cautiously. Sixth, this study compared two complete clinical sedation strategies, remimazolam combined with flumazenil versus etomidate combined with placebo, rather than the direct pharmacological effects of the sedative drugs alone.

# Conclusions

Remimazolam tosilate combined with flumazenil significantly shortened recovery time in older men undergoing procedural sedation for transperineal prostate biopsy, without observed impairment of early cognitive recovery or increased risk of hemodynamic instability. This regimen was associated with a lower incidence of PONV and no observed myoclonus or injection pain. Because this was a single-center trial stopped early for efficacy, these findings require further validation in larger multicenter studies.

# Abbreviations

AE, adverse event; ASA, American Society of Anesthesiologists; BIS, bispectral index; BMI, body mass index; CI, confidence interval; DSST, Digit Symbol Substitution Test; IDMC, independent data monitoring committee; IQR, interquartile range; ISAS, Iowa Satisfaction with Anesthesia Scale; MAP, mean arterial pressure; PACU, post-anesthesia care unit; PONV, postoperative nausea and vomiting; RR, relative risk; SpO2, peripheral oxygen saturation.

# Declarations

**Ethics approval and consent to participate**

This study was conducted in accordance with the Declaration of Helsinki and applicable guidelines and regulations. The study was approved by the Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University (initial approval No. XJTU1AF2024LSYY-368; amended protocol approval No. XJTU1AF2024LSYY-368-04). The final ethics-approved protocol version used for trial conduct was approved before enrollment of the first participant. The study was registered in the Chinese Clinical Trial Registry (ChiCTR2400091993). Written informed consent was obtained from all participants before enrollment.

**Consent for publication**

Not applicable. This study does not contain any identifiable personal information, images, or case details.

**Availability of Data and Materials**

The clinical trial protocol, statistical analysis plan, de-identified dataset, data dictionary, and statistical analysis code supporting this study are available from the

corresponding authors upon reasonable request. The prespecified interim analysis plan and implementation summary are provided as Supplementary File A. Sharing of participant-level data is subject to the requirements of the Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University, participant privacy protections, and applicable data management regulations.

## Competing interests

The authors declare that they have no competing interests.


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## Authors' contributions

Xinyan Chen, Tingting Yang, and Xixi Wang contributed to study design and manuscript drafting. Hailiang Du and Pingyi Song contributed to participant enrollment, clinical implementation, and data collection. Leilei Pei performed the statistical analysis and contributed statistical methodological guidance. Yaomin Zhu and Yansong Li supervised the study, reviewed the manuscript, and revised it for important intellectual content. All authors read and approved the final manuscript.


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**Authors' information**

Not applicable.

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