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CLINICAL TRIAL REPORT

Quality of Postoperative Recovery in Older Patients Undergoing Day Surgery: A Randomized, Non-Inferiority Trial of Remimazolam versus Etomidate for Anesthesia Induction

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Introduction: This study compared the quality of postoperative recovery among older patients undergoing day surgery with induction using remimazolam or etomidate.

Methods: This multicenter, randomized, parallel-group, double-blinded trial with a non-inferiority design was conducted in three tertiary university hospitals. Older patients undergoing day surgery were randomly assigned to receive either remimazolam or etomidate for pump-induced general anesthesia. The primary outcome was the 15-item Quality of Recovery (QoR-15) score on postoperative day 1 (POD1). The mean difference between the groups was compared against a non-inferiority margin of −8. Secondary outcomes included the QoR-15 score on POD2, scores for the five QoR-15 dimensions, and vital signs at predefined time points.

Results: In total, 118 older patients were randomized to the two groups. In the per-protocol set, the QoR-15 score on POD1 was 133.7 ± 12.9 in the remimazolam group, versus 131.2 ± 17.3 in the etomidate group, with a mean difference of 2.5 [95% confidence interval [CI]: −3.2, 8.2). In the modified intention-to-treat set, the QoR-15 scores were 133.5 ± 12.9 and 131.2 ± 17.6 in the remimazolam and etomidate groups, respectively, with a mean difference of 2.3 (95% CI: −3.3, 7.8). The lower limit of the confidence interval exceeded the predefined non-inferiority cutoff of −8, confirming the non-inferiority of remimazolam ($P < 0.001$). We compared the QoR-15 dimension scores on POD1 with the baseline scores in both groups. In the remimazolam group, only the physical independence score on POD1 was higher than at baseline, whereas in the etomidate group, the total QoR-15, physical comfort, physical independence, and emotional state scores were all lower on POD1 than at baseline. During anesthesia maintenance, the remifentanil dosage was higher in the remimazolam group than in the etomidate group (890.1 ± 5.7 μg vs 745.1 ± 45.3 μg, $P = 0.037$).

Conclusion: In older patients undergoing day surgery, remimazolam exhibited non-inferiority to etomidate for anesthesia induction in terms of QoR-15 scores on POD1.

Keywords: remimazolam, etomidate, older patients, postoperative recovery quality, day surgery

Introduction

In 2019, the number of ambulatory surgeries in China reached 1.45 million, accounting for 13.2% of elective operations.[1] With societal aging, the proportion of older patients undergoing ambulatory surgeries is also increasing each year.[2] Older patients exhibit reduced organ function and several co-morbidities, leading to a higher incidence of postoperative complications than noted in younger patients.[3–6] Hemodynamic fluctuations during or after anesthesia induction comprise a common cause of poor postoperative recovery in older patients. Therefore, most anesthesiologists prefer etomidate over propofol as the

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induction anesthetic given its stable hemodynamic characteristics.[7] However, etomidate exerts an inhibitory effect on adrenal function, and it can cause muscle tremors and stiffness and increase postoperative nausea and vomiting, which collectively hamper postoperative recovery.[8–11]

Remimazolam is an ultra-short-acting benzodiazepine that exhibits hemodynamic stability during anesthesia induction with no evidence of adrenal function inhibition.[12–14] If remimazolam can provide similar hemodynamic stability and postoperative recovery as etomidate, then it could emerge as a new option for anesthesia induction in older patients during day surgery. To date, no study has compared the differences in postoperative recovery between etomidate and remimazolam in older patients following ambulatory surgery. Thus, a direct head-to-head non-inferiority randomized controlled trial is warranted. Meanwhile, as remimazolam is a benzodiazepine, its effect on postoperative delirium remains controversial. Guidelines based on observational studies recommend that preoperative benzodiazepine use should be avoided in older patients to prevent postoperative complications such as delirium.[15,16] However, a large randomized controlled trial involving 909 older patients undergoing non-cardiac surgery found that routine preoperative intravenous midazolam injection did not increase the incidence of postoperative delirium.[17] Moreover, some studies demonstrated that preoperative benzodiazepine use alleviated patients' anxiety and potentially improved patients' satisfaction.[18,19] Remimazolam, unlike other benzodiazepines (eg, midazolam), can replace propofol or etomidate as a single sedative hypnotic combined with opioids for general anesthesia induction. Further study is needed to clarify whether a single induction dose will increase postoperative delirium in older patients and affect the quality of postoperative recovery. Therefore, a multicenter, randomized, parallel-controlled, double-blind study was designed to explore the non-inferiority of remimazolam-induced laryngeal mask general anesthesia in older patients in comparison with etomidate in terms of recovery quality and postoperative adverse events after day surgery.

Methods

Ethics and Recruitment

The study was approved by the Ethics Committees of Xijing Hospital of Air Force Military Medical University (KY20222277-F-1), Xi'an People's Hospital (KJLL-H-K-2023014), and Affiliated Hospital of Yan'an University (YAS-H01-202307008) and registered with ClinicalTrials.gov (registration date: January 29, 2023; registration number: NCT05748665). This study was conducted in compliance with the guidelines of the Declaration of Helsinki. After obtaining written informed consent from all patients, the trial was conducted from August 2023 to January 2024. Older patients (≥60 years) with American Society of Anesthesiologists (ASA) physical status I–III and body mass index (BMI) of 18–30 kg/m^2 were eligible. These patients were scheduled to receive laryngeal mask general anesthesia for day surgery. Patients with cognitive dysfunction, neuropsychiatric disorders, benzodiazepine or opioid use within 1 month preoperatively, estimated difficult airways, adrenocortical insufficiency, porphyria, a history of chronic corticosteroid therapy, and known contraindications or allergies to benzodiazepines, opioids, or etomidate or its components were excluded.

Interventions and Anesthesia

This multicenter, randomized, parallel-group trial with a non-inferiority design was conducted in three tertiary university hospitals. A doctor who was not involved in data management and statistical analyses generated the random number sequence using Depax EDC (DAP Software, Beijing, China). Randomization was conducted using a 1:1 allocation ratio, and enrollment was conducted by the research center. Subjects were blinded to the induction agent used. Blinded researchers performed screening, recruitment, data collection, mask ventilation, laryngeal mask insertion, and outcome evaluation. Unblinded nurses prepared and administered the drugs, while concealing the syringe, syringe pump, and intravenous catheter during the infusion process.

The patients received remimazolam or etomidate at a dose of 0.2 mg/kg within 1 min depending on their grouping. When the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score was <2, sufentanil (0.2 μg/kg) and rocuronium (0.6 mg/kg) were intravenously administered. Conversely, if the MOAA/S score was 2 or higher, 0.5–1 mg/kg propofol was used as a rescue hypnotic. The laryngeal mask was placed 2 min after anesthesia induction. Sevoflurane and remifentanil were used in both groups to maintain the anesthesia index (Ai) between 40 and 60 (ConView system,

version 2.4.1, Pearlcare Medical Technology Company Limited, Zhejiang, China), with rocuronium added as required. Vasoactive drugs were administered as needed to maintain patients' blood pressure and heart rate (HR) within 20% of the baseline values.

No premedication was given before anesthesia. Upon entering the operating theater, standard monitoring was commenced, including electrocardiogram (ECG), pulse oximetry, non-invasive or invasive blood pressure measurement, and anesthesia depth assessment. All patients were given nonsteroidal anti-inflammatory drugs and local incision infiltration for analgesia, along with antiemetics to prevent postoperative nausea and vomiting. Neostigmine or sugammadex was provided as necessary to antagonize residual muscarinic effects. The return of consciousness (ROC) was confirmed by removing the laryngeal mask, with ROC defined as the patient's response to verbal commands and sufficient spontaneous respiration, following which the patient was transferred to the post-anesthesia care unit (PACU).

Outcome and Measurements

The primary aim of this study was to evaluate the quality of postoperative recovery using the 15-item Quality of Recovery (QoR-15) questionnaire, a comprehensive measure of postoperative recovery that encompasses five dimensions: physical comfort (five items), emotional state (four items), physical independence (two items), psychological support (two items), and pain (two items). Each item was scored on an 11-point scale, with higher scores indicating more frequent positive responses and lower scores indicating more frequent negative responses. The total score ranged from 0 (worst recovery) to 150 (best recovery). Patients completed the QoR-15 questionnaire 1 day before surgery and on postoperative days (PODs) 1 and 2, with the POD1 score serving as the primary outcome.

Additional assessments were conducted to comprehensively evaluate perioperative outcomes. These included the QoR-15 scores across all five dimensions on POD1 and POD2 and the total QoR-15 score on POD2. The time to loss of consciousness and the incidence of muscle fibrillation and injection pain during anesthesia induction were also measured. Hemodynamic parameters, including mean arterial pressure (MAP), HR, and SpO_2, were monitored at multiple time points: before induction, 1 min after induction, 1 min after laryngeal mask placement, and at the start of the procedure. Ai was also recorded at predefined time points. Other key metrics included the operative and anesthesia times, the awakening time, and the total amount of anesthetics used. The incidence of adverse events in the PACU, covering postoperative nausea and vomiting, hypoxia ($SpO_2 < 90\%$), hemodynamic fluctuations (>20% of baseline), bradycardia (HR < 50 beats/min), and intraoperative awareness [defined as the patient voluntarily recalling and reporting what happened during general anesthesia or elicited by the doctor using prescribed questioning phrases (modified Brice questionnaire)], was documented. The occurrence of delirium during the PACU period was evaluated using the Confusion Assessment Method-Severity scale.

Statistical Analysis

The primary outcome of the study was the quality of recovery after surgery, as assessed by the QoR-15 score. Previous studies[20] suggested that the minimal clinically important difference is 8. Therefore, the non-inferiority margin for the mean difference between the groups was set at −8. Based on previous studies, the standard deviation of the QoR-15 score was 14. Considering a dropout rate of 15%, a sample size of 118 was calculated to achieve 90% power with a type I error rate of 0.05.

Data management was conducted using Depax EDC. Statistical analyses were performed using SPSS 26.0 software (IBM, Armonk, NY, USA). All graphs were generated using GraphPad Prism 5.0 software (GraphPad Inc., Boston, MA, USA). For statistical assessments, a two-tailed test was applied, and $P < 0.05$ indicated statistical significance. The normality of the data was assessed using the Kolmogorov–Smirnov test. Normally distributed data were presented as the mean ± standard deviation, skewed data were presented as the median, and count data were presented as frequencies and percentages. For baseline variables such as age, sex, BMI, the ASA classification, the surgical site, the surgical duration, and the age-adjusted Charlson Comorbidity Index (ACCI), between-group differences were examined using Student's *t*-test for normally distributed continuous variables, the Mann–Whitney *U*-test for non-normally distributed variables, and the chi-squared test or Fisher's exact probability method for categorical variables. The primary outcome was compared between the groups using the Mann–Whitney *U*-test in both the modified intention-to-treat (mITT) and per-protocol (PP) analysis sets. For subgroup analyses, the

baseline variables included age, sex, BMI, ACCI, and the study center. A generalized linear model was used to test the interaction between the effect of the two drugs on quality of postoperative recovery and the five subgroup variables. For intraoperative repeated-measures variables such as systolic and diastolic blood pressure, MAP, HR, and Ai, repeated-measures analysis of variance or a generalized linear mixed model (GLMM) was used on the basis of the results of the Kolmogorov–Smirnov test. In the GLMM, the patient was set as a random variable, and the induced drug group, time, and the drug group–time interaction were set as fixed variables.

Results

In total, 162 older patients who underwent outpatient surgery between August 2023 and January 2024 were screened, and 44 patients were excluded because of ineligibility, refusal to participate, or surgery cancellation. Finally, 118 patients were randomly assigned at a 1:1 ratio to the remimazolam or etomidate group. In the remimazolam group, laryngeal mask placement failed in two patients, and they were thus converted to endotracheal intubation. In addition, two patients were lost to follow-up. In the etomidate group, one patient used patient-controlled analgesia (Figure 1). Therefore, the mITT analysis set consisted of 116 patients (57 remimazolam, 59 etomidate), 113 of whom were included in the PP analysis set. The baseline data of all patients in the mITT analysis set revealed that demographic data, smoking history, comorbidities, type of surgery, study center, ACCI, and the Apgar score were all balanced and comparable between the groups (Table 1).

The results for both the PP and mITT analysis sets for the primary outcome confirmed the non-inferiority of remimazolam to etomidate. In the PP set, the QoR-15 score was 133.7 ± 12.9 in the remimazolam group, versus

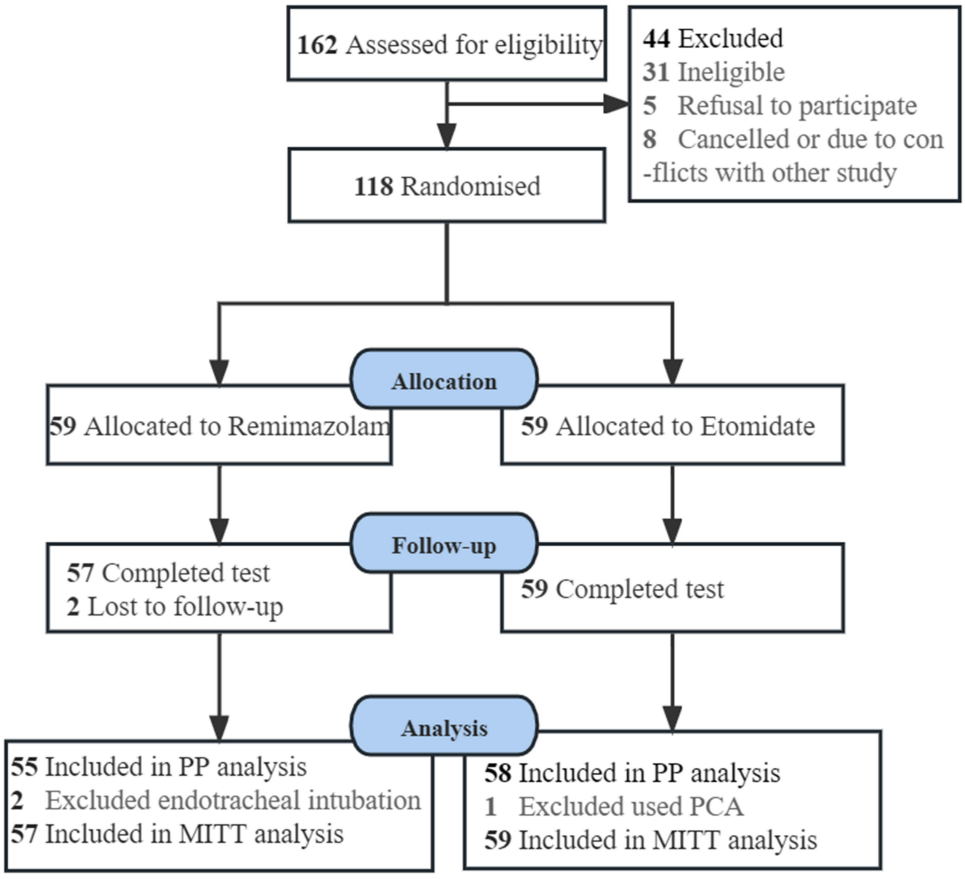

Figure 1 Flowchart of patient enrollment. In total, 162 patients were screened for the study, and 118 patients were finally randomized. In the remimazolam group, laryngeal mask placement failed in two patients, and these patients were thus converted to endotracheal intubation. In addition, two patients were lost to follow-up. In the etomidate group, one patient used patient-controlled analgesia. The mITT set included 57 patients in the remimazolam group and 59 patients in the etomidate group. In the PP set, 55 patients were assigned to the remimazolam group, and 58 patients were assigned to the etomidate group.
Abbreviations: mITT, modified intention-to-treat; PP, per-protocol; PCA, patient-controlled analgesia.

Table 1 Baseline Information of the mITT Analysis Set

Variables	Remimazolam (n = 57)	Etomidate (n = 59)	*P*
Sex			0.398
Male	42 (71.1%)	46 (77.9%)	
Female	17 (28.8%)	13 (22.0%)	
Age (years)	68.75 ± 5.41	69.85 ± 5.98	0.296
Height (cm)	165.93 ± 7.112	167.22 ± 7.557	0.746
Weight (kg)	64.90 ± 11.167	65.25 ± 7.881	0.755
BMI	23.46 ± 3.087	23.35 ± 2.557	0.139
ASA			0.181
I	1 (1.69%)	3 (5.08%)	
II	47 (79.66%)	51 (86.44%)	
III	11 (18.65%)	5 (8.48%)	
Smoking	28 (47.4%)	33 (55.9%)	0.357
Complication			>0.999
Hypertension	18 (30.5%)	20 (33.8%)	
Cerebral peduncle	10 (16.9%)	7 (11.8%)	
Coronary heart disease	9 (15.2%)	2 (3.3%)	
Diabetes	6 (10.1%)	9 (15.2%)	
Lung diseases	4 (6.7%)	3 (5%)	
Kidney disease	2 (3.3%)	1 (1.6%)	
Digestive system diseases	5 (8.4%)	2 (3.3%)	
Types of surgery			>0.999
Cholecystectomy	19 (32.2)	21 (35.6%)	
Hernia repair surgery	37 (62.7%)	35 (59.3%)	
Other	3 (5.1%)	2 (3.4%)	
Center			0.981
Xijing Hospital	44 (74.6%)	48 (81.4%)	
Affiliated Hospital of Yan'an University	10 (16.9%)	6 (10.2%)	
Xi'an People's Hospital	5 (8.4%)	5 (8.4%)	
ACCI	3.66 ± 1.40	4.17 ± 1.78	0.087
Apgar score	9.05 ± 0.117	9.02 ± 0.161	0.529
Preoperative QoR-15 score	133.3 ± 12.8	137.6 ± 10.1	0.518

Notes: Data are expressed as the mean ± standard deviation or n (%). The Apgar score predicts mortality within 30 days after surgery and assesses the risk of postoperative complications after general or vascular surgery.
Abbreviations: ACCI, age-adjusted Charlson Comorbidity Index; ASA, American Society of Anesthesiologists; BMI, body mass index; mITT, modified intention-to-treat; QoR-15, 15-item Quality of Recovery.

131.2 ± 17.3 in the etomidate group, with a mean difference of 2.5 [95% confidence interval [CI]: −3.2, 8.2). In the mITT set, the QoR-15 scores were 133.5 ± 12.9 and 131.2 ± 17.6 in the remimazolam and etomidate groups, respectively, with a mean difference of 2.3 (95% CI: −3.3, 7.8). In both analyses, the lower limit of the confidence interval exceeded the predefined non-inferiority cutoff of −8, confirming the non-inferiority of remimazolam ($P < 0.001$, Figure 2). The results of the subgroup and interaction analyses for the primary outcome metrics are presented in Figure 3. The effects of remimazolam and etomidate on the quality of recovery after general anesthesia delivered via a laryngeal mask in older patients did not significantly differ concerning age, sex, BMI, ASA classification, and study center. In addition, no significant interaction was noted between the effect of remimazolam or etomidate on the quality of postoperative recovery and any of the subgroup variables.

The secondary outcome indicators were analyzed in the PP set. The total QoR-15 score on POD2 was 135.9 ± 16.5 in the remimazolam group and 137.0 ± 12.7 in the etomidate group, giving a mean difference of −1.1 (95% CI: −6.6, 4.4), revealing no significant difference between the groups ($P = 0.198$). Analysis of the postoperative QoR-15 scores of the five dimensions revealed no interaction effect between group and time ($P > 0.05$). A significant time effect ($P < 0.05$)

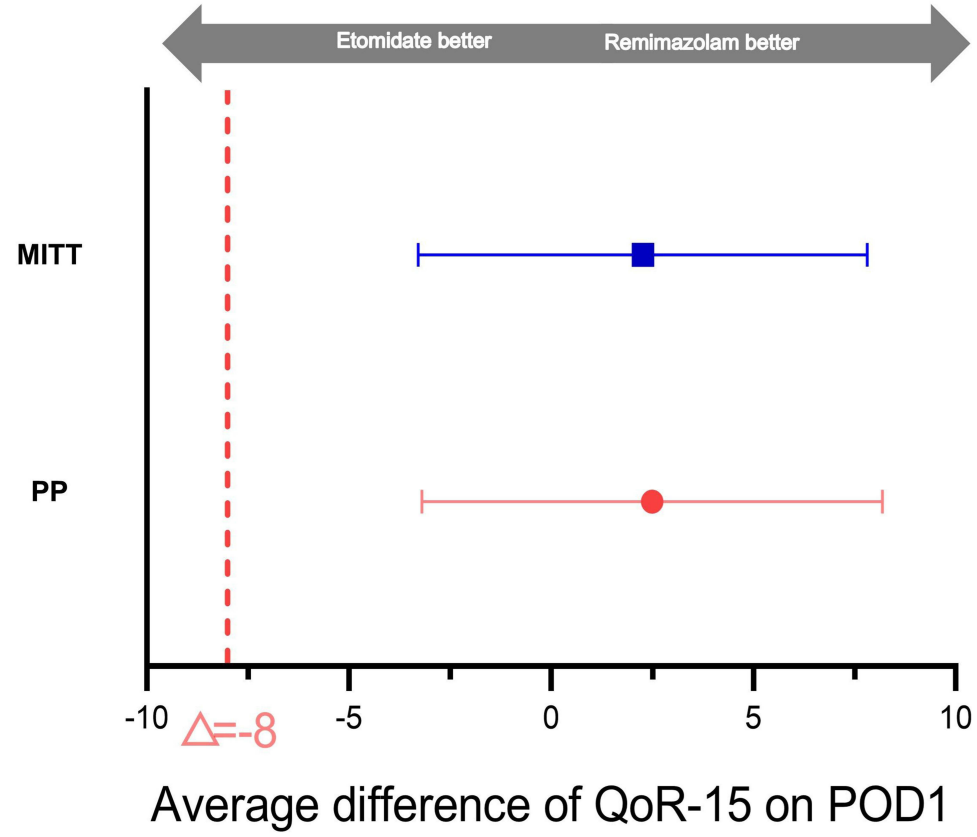

Figure 2 Non-inferiority plot of the QoR-15 score on POD1. Data are expressed as the mean ± 95% confidence interval. The vertical line at −8 indicates the non-inferiority margin of the QoR-15 score in this population. Δ, non-inferiority margin.
Abbreviations: QoR-15, 15-item Quality of Recovery; POD1, postoperative day 1.

Subgroup	Etomidate	Remimazolam	LS Mean Difference (95% CI)	P	P'
All Patients	58	55	2.26 (-3.10, 7.62)	0.41	
Age					0.393
< 70	26	40	4.28 (-3.30, 11.86)	0.273	
≥ 70	31	15	-0.58 (-8.95, 7.79)	0.892	
Sex					0.544
Male	45	40	0.77 (-4.02, 5.57)	0.753	
Female	13	15	4.93 (-10.85, 20.71)	0.545	
ASA					0.484
I	3	0			
II	50	43	3.38 (-2.80, 9.56)	0.286	
III	5	12	-3.89 (-15.31, 7.53)	0.515	
BMI					0.311
< 28	53	47	3.19 (-2.71, 9.10)	0.291	
≥ 28	5	8	-5.65 (-15.55, 4.25)	0.29	
Center					0.981
Xijing Hospital	43	45	2.21 (-2.96, 7.39)	0.405	
Affiliated Hospital of Yan 'an University	10	5	-0.04 (-35.36, 35.29)	0.998	
Xi 'an People's Hospital	5	5	3.33 (-8.00, 14.65)	0.583	

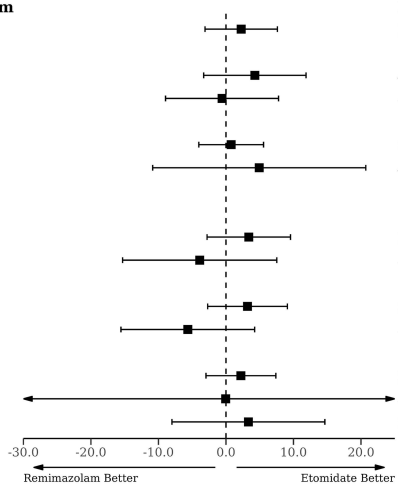

Figure 3 Forest map of QoR-15 subgroup analysis on postoperative day 1.
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; LS mean, least squares mean; mITT, modified intention-to-treat; PP, per-protocol; P', Bonferroni-corrected *P* value.

was observed for all dimensions excluding psychological support ($P = 0.088$). The scores for the five dimensions did not significantly differ between two groups on POD1 and POD2 (Table 2). Upon analyzing the within-group differences, only the physical independence scores on POD1 and POD2 were lower than the baseline score in the remimazolam group ($P < 0.05$), whereas the scores for the remaining four dimensions (pain, physical comfort, psychological support, and

Table 2 Total QoR-15 Scores and Scores for the Five Dimensions

Variables	Remimazolam (n = 55)	Etomidate (n = 58)	Median Difference (95% CI)	Mixed-Time Effect *P*		
				Group	Time	Group–Time
Pain				0.895	0.004	0.766
Baseline	19.3 ± 3.1	19.5 ± 2.1	−0.2 (−1.2, 0.7)			
POD1	18.4 ± 3.1	17.9 ± 3.7	0.4 (−0.9, 1.7)			
POD2	17.8 ± 4.2	18.4 ± 2.9	−0.6 (−1.9, 0.7)			
Physical comfort				0.595	0.027	0.542
Baseline	43.3 ± 5.1	43.9 ± 5.4	−0.6 (−2.6, 1.4)			
POD1	42.1 ± 6.9	41.5 ± 7.1	0.7 (−1.9, 3.3)			
POD2	42.2 ± 6.9	45.3 ± 5.4	−3.1 (−5.4, −0.8)			
Physical independence				0.866	0.001	0.558
Baseline	17.8 ± 2.1	18.2 ± 1.8	−0.4 (−1.2, 0.3)			
POD1	16.8 ± 2.9	16.7 ± 3.3	0.1 (−1.0, 1.3)			
POD2	17.5 ± 3.1	17.8 ± 2.5	−0.4 (−1.4, 0.7)			
Psychological support				0.522	0.088	0.511
Baseline	18.6 ± 2.2	18.8 ± 1.8	−0.2 (−0.9, 0.6)			
POD1	18.8 ± 1.8	18.4 ± 2.3	0.5 (−0.3, 1.2)			
POD2	18.8 ± 1.7	19.0 ± 1.6	−0.3 (−0.9, 0.3)			
Emotions				0.553	0.011	0.144
Baseline	36.4 ± 4.9	37.3 ± 3.7	−0.9 (−2.5, 0.7)			
POD1	37.6 ± 2.7	36.1 ± 4.3	0.9 (−0.5, 2.1)			
POD2	37.8 ± 3.9	38.1 ± 3.1	−0.4 (−1.7, 1.0)			

Abbreviations: CI, confidence interval; POD, postoperative day; QoR-15, 15-item Quality of Recovery.

emotional state) did not significantly differ between POD1 and baseline (all $P > 0.05$). Conversely, in the etomidate group, the QoR-15 score and the physical independence, physical comfort, and emotional state scores were lower on POD1 than at baseline (all $P < 0.05$, Figure 4). We compared the changes in the total QoR-15 scores and the five dimension scores from baseline to POD1 between the remimazolam and etomidate groups and found that the change in the emotional score significantly differed between the two groups ($P = 0.036$, Table S1).

No patients required remedial analgesia or sedation during the induction period. The time to loss of consciousness was similar between the remimazolam and etomidate groups (97.7 ± 4.1 s vs 97.5 ± 5.1 s; $P = 0.87$). Muscle fibrillation, which refers to involuntary twitching of muscle fibers, occurred in three patients in the remimazolam group and two patients in the etomidate group. The anesthesia duration, surgery duration, awakening time, intraoperative urine volume, and intraoperative rehydration volume did not significantly differ between the groups (all $P > 0.05$). Regarding the dosage of anesthetic drugs, the remifentanil dosage was significantly higher in the remimazolam group (890.12 ± 5.738 μg) than in the etomidate group (745.09 ± 45.320 μg, $P = 0.037$, Table 3). Considering the hemodynamic changes and Ai during the induction period, no differences were observed between the two groups at the predefined time points (Figure S1).

In the PACU, delirium occurred in four patients in the remimazolam group and two patients in the etomidate group ($P > 0.05$). Adverse events other than delirium in the PACU were also recorded. In the remimazolam group, the adverse events included nausea and vomiting in five patients, hypoxemia in one patient, and drowsiness in one patient. Meanwhile, six patients in the etomidate group experienced adverse events, including nausea in vomiting, blood pressure fluctuation, and drowsiness in four, one, and two patients, respectively (Table 3). Intraoperative awareness was not reported in either group.

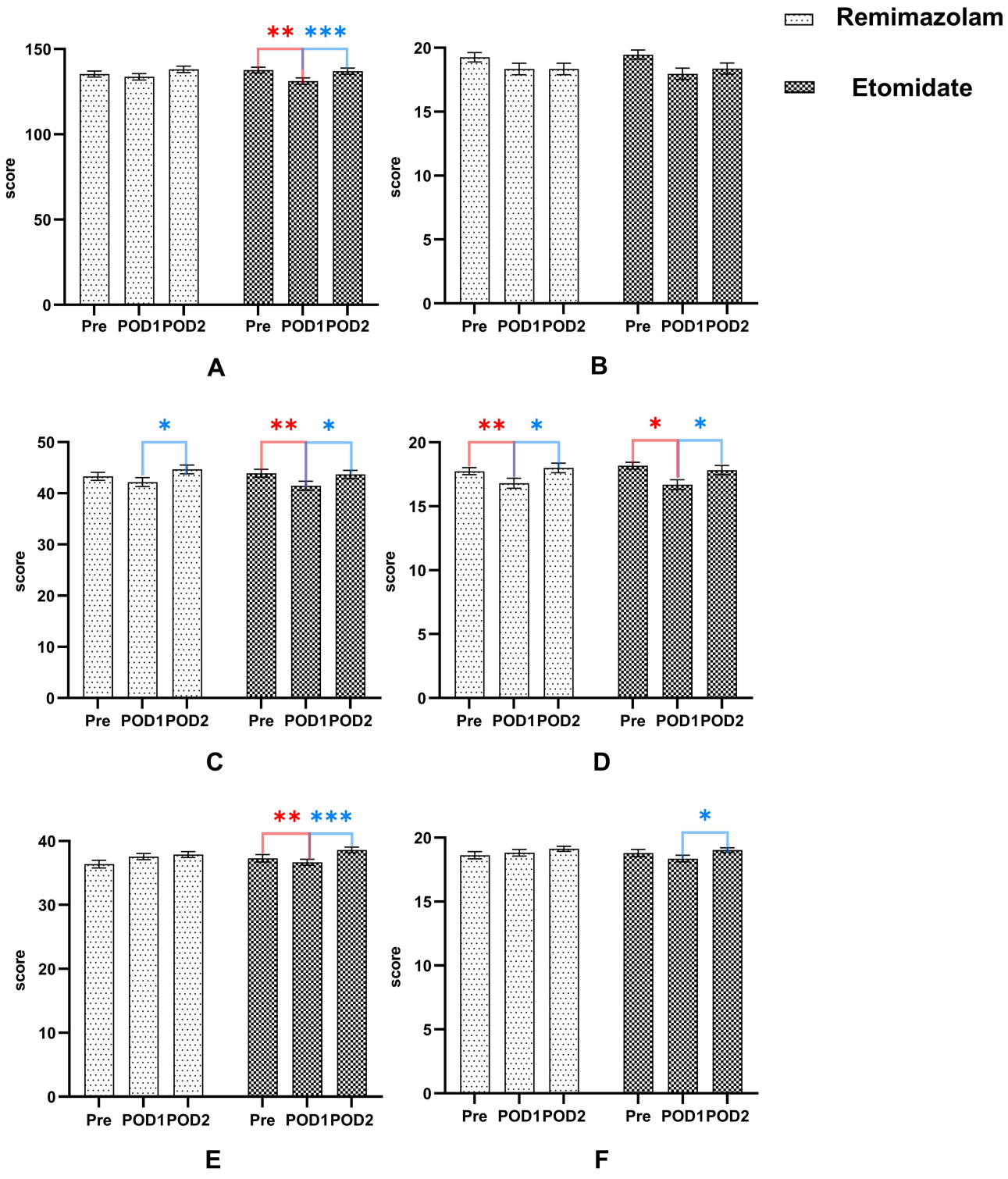

Figure 4 Total QoR-15 score and scores for the five dimensions at different time points within each group. (**A**) QoR-15 score; (**B**) Pain score; (**C**) Physical comfort score; (**D**) Physical Independence score; (**E**) Emotional state score; (**F**) Psychological support score. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Red*, comparison between POD1 and baseline; Blue*, comparison between POD2 and POD1.

Abbreviations: POD, postoperative day; QoR-15, 15-item Quality of Recovery.

Table 3 Intraoperative Data and Adverse Effects in the PACU

Variables	Remimazolam (n = 55)	Etomidate (n = 58)	*P*
Time to loss of consciousness (s)	97.7 ± 4.1	97.5 ± 5.1	0.87
Injection pain	0	0	/
Muscle fibrillation	3 (5.1%)	2 (3.4%)	0.648
Use of vasoactive drugs			
Induction of anesthesia	6 (10.2%)	2 (3.4%)	0.143
Maintenance of anesthesia	43 (72.9%)	39 (66.1%)	0.424
Duration of anesthesia (min)	110.1 ± 4.89	110.3 ± 5.9	0.574
Duration of surgery (min)	80.1 ± 4.7	75.8 ± 5.1	0.262
Recovery time (min)	18.2 ± 1.2	22.5 ± 3.4	0.935
Fluid infusion (mL)	967.8 ± 33.4	1003.4 ± 23.1	0.251
Urine output (mL)	27.0 ± 15.7	11.91 ± 7.7	0.778
Dosage of anesthetic drugs, (μg)			
Sufentanil	20.6 ± 0.7	20.8 ± 0.8	0.804
Remifentanil	890.1 ± 5.7	745.1 ± 45.3	0.037
Delirium in the PACU	4 (6.7%)	2 (3.5%)	0.402
Adverse events in the PACU	7 (11.8%)	6 (10.2%)	0.485
Nausea and vomiting	5 (8.4%)	4 (6.7%)	
Hypoxia	1 (1.6%)	0	
Blood pressure fluctuations	0	1 (1.6%)	
Bradycardia	0	0	
Intraoperative awareness	0	0	
Sleepiness	1 (1.6%)	2 (3.4%)	

Note: Data are described as the mean ± standard deviation or n (%).
Abbreviation: PACU, post-anesthesia care unit.

Discussion

In this multicenter, randomized controlled, double-blind trial, we compared the quality of postoperative recovery in older patients receiving remimazolam or etomidate for laryngeal mask general anesthesia for day surgery. The results indicated that the quality of postoperative recovery in the remimazolam group was non-inferior to that in the etomidate group. In particular, only the physical independence score was lower on POD1 than at baseline in the remimazolam group; conversely, in the etomidate group, the total QoR-15 score and the physical comfort, physical independence, and emotional state scores were lower on POD1 than at baseline.

Increasing attention is being paid to patient-reported outcomes after outpatient surgery, with patients' subjective well-being and satisfaction prioritized as important outcomes. The QoR-15 score is recommended for assessing the quality of recovery in the early postoperative period in the United States, as outlined in the Joint Statement for Enhancing Quality of Recovery in the Perioperative Period.[21] Given the rapid recovery typically observed after day surgery, we chose the QoR-15 score to describe the recovery profile of our patients. Our results indicated that remimazolam was non-inferior to etomidate as a general anesthesia hypnotic for older patients undergoing day surgery, and remimazolam performed better in some dimensions, such as physical comfort, physical independence, and emotional state. Our results were similar to prior findings that remimazolam achieved better psychological support scores than propofol in patients undergoing ambulatory surgery.[22] We speculated that the results were related to the anxiolytic and retrograde amnesia effects of benzodiazepines such as remimazolam. These properties of benzodiazepines might help reduce anxiety and improve the subjective well-being of patients, particularly those with severe levels of anxiety or depressive tendencies. Therefore, older patients with these conditions might benefit from remimazolam as a premedication or induction agent. However, the dimension-specific QoR-15 findings should be cautiously interpreted because these variables were not primary outcomes. Future studies should consider evaluating both the total QoR-15 score and the changes in each dimension score versus baseline. This approach will provide a more comprehensive understanding of the impact of different anesthetic agents on postoperative recovery. Despite the absence of significant

interaction effects for factors such as age, sex, BMI, or the ASA status in our subgroup analysis, a significant demographic imbalance existed, as the remimazolam group featured fewer patients older than 70 years. This discrepancy represents a potential source of bias.

Our study recorded slightly higher remifentanil consumption in the remimazolam group than in the etomidate group, a result that contradicts a previous study by Guan et al[23] involving tracheal intubation. This divergence might stem from our use of a lower remimazolam dose, justified by the reduced stress of laryngeal mask insertion versus intubation. The hemodynamic stability achieved with remimazolam could have also diminished analgesic synergy. Future research is needed to clarify the remimazolam–opioid interaction.

Postoperative delirium tends to occur in older patients undergoing surgery, and benzodiazepine use has been associated with delirium. To our knowledge, there is no evidence suggesting that remimazolam increases the incidence of postoperative delirium because it is rapidly metabolized and is not metabolized by the liver or kidneys.[24] In Liao et al's study,[25] remimazolam reduced early postoperative cognitive dysfunction in older patients, and this effect might be related to the reduction of the inflammatory response. In this study, the incidence of emergency delirium was comparable between the groups; however, it cannot be concluded that remimazolam does not increase the incidence of delirium for longer periods (eg, 1 week) postoperatively, and the relevant conclusions need to be clarified in further studies.

In this study, the Ai was used to assess the depth of anesthesia, and we found that this index could accurately predict changes in consciousness during remimazolam anesthesia and reasonably and accurately monitor the depth of anesthesia.

Several limitations of this study warrant consideration. First, although the study had a multicenter design and patients were enrolled from three institutions, the significant disparities in enrollment numbers across centers might have introduced selection bias and compromised population representation. Second, the rapid discharge protocol characteristic of ambulatory surgeries necessitated telephonic follow-ups for 52.3% of patients. This data collection method, combined with varying health literacy levels in patients, might have introduced recall bias and information inaccuracies despite the implementation of investigator blinding procedures. Third, as the patients' short hospital stays made in-person visits on POD3 unfeasible, our assessment of delirium was limited to the PACU period. Finally, our findings were specific to geriatric populations undergoing low-risk ambulatory procedures, in which the observed minimal deviation from preoperative baseline recovery scores likely reflects the inherent advantages of minimally invasive outpatient surgery protocols. Consequently, the generalizability of remimazolam's recovery profile to major invasive surgeries (eg, oncological resections or cardiovascular procedures) remains to be established through prospective trials with extended postoperative observation periods.

Conclusions

This study established the non-inferiority of remimazolam versus etomidate for postoperative recovery and its favorable mood profile in older patients undergoing ambulatory surgery.

Abbreviations

ASA, American Society of Anesthesiologists; ACCI, age-adjusted Charlson Comorbidity Index; AI, anesthesia depth index; GLMM, generalized linear mixed model; HR, heart rate; MOAA/S, Modified Observer's Assessment of Alertness/Sedation; MAP, mean arterial pressure; mITT; modified intention-to-treat; POD, postoperative day; PP, per-protocol; PACU, post-anesthesia care unit; QoR, Quality of Recovery; ROC, return of consciousness.

Data Sharing Statement

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The study was approved by the Ethics Committee of Xijing Hospital of Air Force Military Medical University (KY20222277-F-1), Xi'an People's Hospital (KJLL-H-K-2023014), and Affiliated Hospital of Yan'an University (YAS-H01-202307008),

and it was registered with ClinicalTrials.gov on January 29, 2023 (NCT05748665). Written informed consent was obtained from all patients prior to enrollment.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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