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ORIGINAL ARTICLE

Sedation Dose of Remimazolam for Older Adults Undergoing Hip Arthroplasty with Neuraxial Anesthesia and Its Impact on Postoperative Delirium

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Abstract

OBJECTIVE: Remimazolam tosylate is an ultra-short-acting benzodiazepine sedative. This study aimed to determine a suitable intraoperative remimazolam dose for older adults undergoing hip arthroplasty with neuraxial anesthesia and to explore its association with postoperative delirium (POD) and perioperative stress responses.

METHODS: In this randomized study, 153 older adults undergoing hip arthroplasty with neuraxial anesthesia were allocated to four groups: saline control (N), remimazolam 0.1 mg/(kg•h) (R1), 0.2 mg/(kg•h) (R2), and 0.3 mg/(kg•h) (R3). Primary outcomes were intraoperative sedation success (modified Observer's Assessment of Alertness/Sedation scale), plasma cortisol and norepinephrine concentrations at operating room entry and exit, and incidence of POD.

RESULTS: In the R2 group, sedation success was 100%, and the mean awakening time was 6.82 ± 0.64 min, shorter than in the R3 group (8.16 ± 0.93 min), which exhibited deeper sedation and longer recovery. No statistically significant differences were observed in POD incidence across groups (2.86–6.00%; $p = 0.922$), and the study was underpowered to detect modest between-group differences. Compared with saline, the remimazolam groups had lower cortisol and norepinephrine concentrations at operating room exit, whereas within-group changes from entry to exit did not reach statistical significance ($p > 0.05$).

CONCLUSION: Compared with saline, the remimazolam groups had lower cortisol and norepinephrine concentrations at operating room exit, whereas within-group changes from entry to exit did not reach statistical significance ($p > 0.05$). Within the observed POD incidence range (2.86–6.00%), remimazolam did not appear to increase POD over the first 7 postoperative days compared with saline, although the study was not powered to detect modest differences.

Abbreviations:

ACEI	- Angiotensin Converting Enzyme Inhibitor
ASA	- American Society of Anesthesiologists
BIS	- Bispectral index
BMI	- Body Mass Index
CAM	- Confusion Assessment Method
Cor	- Cortisol
DSM-5	- Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	- Electrocardiogram
HR	- Heart rate
IC	- Intensive Care Unit
LSD-t	- Least Significant Difference t-test
MAP	- Mean arterial pressure
MOAA/S	- Modified Observer's Assessment of Alertness and Sedation
NE	- Norepinephrine
PCIA	- Patient Controlled Intravenous Analgesia
POD	- Postoperative delirium
SpO2	- Saturation of Peripheral Oxygen
SBP	- Systolic Blood Pressure
3D-CAM	- 3D-Confusion Assessment Method

INTRODUCTION

Artificial hip arthroplasty is among the most effective surgical interventions for end-stage hip diseases, including hip fractures, femoral head necrosis, hip dysplasia, degenerative osteoarthritis of the hip, and rheumatoid arthritis. Approximately 0.83% of the population in the United States has undergone hip arthroplasty (Maradit Kremers *et al.* 2015). With population aging, the demand for orthopedic surgery among older adults continues to increase, and the number of hip arthroplasty procedures is expected to double by 2030 compared with 2023 (Aldecoa *et al.* 2017). Older adults often have reduced tolerance to surgery and anesthesia, which may increase intraoperative stress responses, hemodynamic instability, and postoperative cognitive impairment, compromising perioperative safety and outcomes (Costa-Martins *et al.* 2021; Zhu *et al.* 2023). Reported postoperative delirium incidence after hip arthroplasty in older adults is high, up to 61% (Chang *et al.* 2022).

Neuraxial anesthesia has increasingly been adopted as the preferred anesthetic technique for hip arthroplasty, as it requires smaller drug dosages than general anesthesia, thereby limiting drug accumulation and reducing adverse effects on cardiac and pulmonary perfusion (Desai *et al.* 2018). However, patients remain conscious during surgery under neuraxial anesthesia and may experience nervousness, anxiety, and fear (Sun *et al.* 2023). Therefore, adjunctive moderate sedation is often used in this setting. In older adults undergoing neuraxial hip arthroplasty, sedation requirements are substantial. An optimal sedative should provide patient comfort and demonstrate rapid onset, predictable dose–response, rapid recovery after discontinuation, lack of accumulation, and minimal adverse effects. Remimazolam tosylate, an ultra–short-acting benzodiazepine, exhibits rapid onset and metabolism. It is hydrolyzed by non-specific plasma esterases into pharmacologically inactive metabolites, thereby avoiding drug accumulation (Kilpatrick, 2021; Kim, 2022; Sneyd & Rigby-Jones, 2020; Goudra *et al.* 2020). Its favorable pharmacokinetic profile and minimal side effects make remimazolam a promising agent for older adults. However, evidence regarding its use for sedation during hip arthroplasty under neuraxial anesthesia remains limited. This study therefore aimed to determine a suitable remimazolam maintenance dose for intraoperative sedation in older adults undergoing hip arthroplasty with neuraxial anesthesia and to explore its association with postoperative delirium and perioperative stress responses in this setting.

DATA AND METHODS

Ethics and research participants

Approval for this study was obtained from the Ethics Committee of the Second Hospital of Shanxi Medical University (2025-XY-0079), and informed consent was obtained from all patients or their family members. A total of 153 older adults who underwent elective hip arthroplasty under neuraxial anesthesia between April and July 2025 were enrolled. Eligibility criteria included age ≥ 65 years, body mass index 18–31 kg/m^2, American Society of Anesthesiologists grade II–III, and no prior history of allergy to anesthetic agents. Exclusion criteria were refusal to provide informed consent, coagulation disorders, unplanned transfer to the intensive care unit, known allergy to the study drugs, intolerance to surgery, severe organic lesions, or pre-existing cognitive dysfunction.

Study design

A saline placebo was used as the control, and the primary outcome was intraoperative sedation success in the remimazolam groups, defined as achievement and maintenance of the target MOAA/S score (≤3 points) without meeting predefined criteria for sedation failure. The sample size for the experimental groups was calculated based on relevant literature and prior pilot studies (Zhang *et al.* 2021; Rex *et al.* 2021). The assumed success rates were 94% for the low-dose group, 98% for the medium-dose group, and 90% for the high-dose group. The chi-square trend test (quadratic polynomial weight) was applied to assess the dose–response relationship. With $\alpha = 0.05$ and power > 99%, a minimum of 30 participants per experimental group was required to detect a comparative advantage.

The sample size for the blank control group was determined according to relevant literature, with a planned allocation ratio of 2:1 between the experimental and saline groups, resulting in a requirement of 45 participants in the saline group (Rex *et al.* 2021). Accounting for a potential dropout rate of 15%, the adjusted sample size was 35 participants for each experimental group and 52 participants for the saline group, yielding a total planned enrollment of 157 participants.

Randomization was conducted using a random number method, resulting in four groups: blank control group (N group), low-dose remimazolam tosylate 0.1 mg/(kg•h) group (R1 group), medium-dose remimazolam tosylate 0.2 mg/(kg•h) group (R2 group), and high-dose remimazolam tosylate 0.3 mg/(kg•h) group (R3 group).

Because sedation differed markedly between the saline and remimazolam groups, anesthesiologists performing intraoperative assessments could not be blinded. A single-blind design was therefore used: patients, postoperative assessors, and statisticians were blinded to group allocation, including personnel responsible for postoperative follow-up and statistical analysis. However, personnel responsible for postoperative follow-up and statistical analysis were blinded to group allocation. The remimazolam tosylate used in this study was produced by Jiangsu Hengrui Pharmaceuticals Co., Ltd. The specification was 36 mg per vial (brand name: Ruibeining), and the batch number was 250518AP.

Patients were instructed to fast and abstain from oral intake for at least 8 hours before surgery. Upon entering the operating room, oxygen was administered via nasal cannula at a flow rate of 3 L/min. Peripheral venous access was established, and 2 ml of venous blood was collected for measurement of plasma cortisol (Cor) and norepinephrine (NE) concentrations. Standard monitoring included electrocardiography and peripheral oxygen saturation (SpO_2). Radial artery puncture and catheterization were performed to enable continuous invasive blood pressure monitoring, and sodium lactate Ringer's solution was infused at a rate of 5–7 ml/kg/h. Neuraxial anesthesia was performed in all patients by the same experienced anesthesiologist: Patients were positioned with the affected side upward in the knee–chest position, and skin preparation and draping were completed. The L_{3-4} or L_{2-3} interspace was selected for subarachnoid puncture.

After confirmation of cerebrospinal fluid withdrawal, light-specific gravity ropivacaine (prepared with 1 ml sterile water for injection and 2 ml of 1% ropivacaine hydrochloride) was injected at a volume of 2.0–3.0 ml, with the anesthesia level maintained between T_8-T_{10}. During skin preparation and draping, 5 ml of normal saline was administered to the N group (injected within 1 minute); Patients in the remimazolam groups (R1, R2, and R3) received an initial dose of 5 mg remimazolam tosylate (diluted to 1 mg/ml and injected within 1 minute). Continuous intravenous infusion of normal saline at 0.5 ml/(kg•h) was administered in the N group until the end of surgery. Sedation levels in the remimazolam groups were assessed using the modified Observer's Assessment of Alertness and Sedation (MOAA/S) scale. When the MOAA/S score exceeded 3 points, intermittent remedial doses of remimazolam tosylate (2.5 mg each, at intervals ≥ 3 minutes) were administered until MOAA/S ≤ 3 points. Sedation failure was defined as persistence of MOAA/S ≥ 4 despite administration of rescue doses totaling more than the initial loading dose. Once adequate sedation was achieved, remimazolam tosylate was infused at rates of 0.1 mg/(kg•h) in the R1 group, 0.2 mg/(kg•h) in the R2 group, and 0.3 mg/(kg•h) in the R3 group. Blood pressure was maintained within 20% of the baseline values (measured after operating room entry and prior to neuraxial anesthesia).

If hypotension occurred (systolic blood pressure [SBP] < 90 mmHg or < 80% of baseline), 6 mg of ephedrine was administered intravenously. Hypertension (SBP > 120% of baseline) was managed with 0.2 mg of nicardipine intravenously, while bradycardia (heart rate < 45 beats/min) was treated with 0.5 mg of atropine intravenously. Hypoxemia (SpO_2 < 90%) was corrected with jaw-lift maneuvers or facial mask oxygen administration. Sedation failure was defined as uncorrectable hypotension (persistent downward SBP trend for > 10 minutes, SBP < 90 mmHg despite fluid resuscitation and three consecutive vasopressor administrations or mean arterial pressure [MAP] decrease > 25% of baseline) or hypoxemia (SpO_2 < 90% lasting > 1 minute despite positive-pressure ventilation with a facial mask). In such cases, remimazolam infusion was discontinued immediately, and symptomatic treatment was provided. In the absence of these conditions, remimazolam infusion was discontinued at the end of surgery. After completion of the procedure, 2 ml of venous blood was again collected for measurement of Cor and NE concentrations.

Postoperatively, all patients received patient-controlled intravenous analgesia with sufentanil (1 μg/kg, diluted with 100 ml normal saline), administered at a continuous rate of 2 ml/h with a lock-out interval of 15 minutes for 48 hours.

The number of remediations with sedative administrations, occurrences of nausea and vomiting, hypotension (SBP<90 mmHg, or MAP decrease greater than 25% of basic value), and hypoxemia (SpO_2 < 90%), and the awakening time (time from drug discontinuation to MOAA/S=5 points) were recorded. The 3D Confusion Assessment Method (3D CAM) was applied twice daily on postoperative days 1, 2, 3, 5, and 7 to assess the occurrence of postoperative delirium (POD), which was defined as fulfillment of the 3D CAM diagnostic algorithm at any assessment within the first 7 postoperative days..

Evaluation indicators

1. MOAA/S score: the MOAA/S scores were sequentially recorded at the following time points prior to anesthesia (T0), after fixation of the anesthesia plane (T1), initiation of drug infusion (T2), 15 minutes after infusion (T3), 30 minutes after infusion (T4), 1 hour after infusion (T5), and at the end of the operation (T6). These measurements were used to assess sedation depth. The MOAA/S scale ranges from 0–5, with lower scores indicating

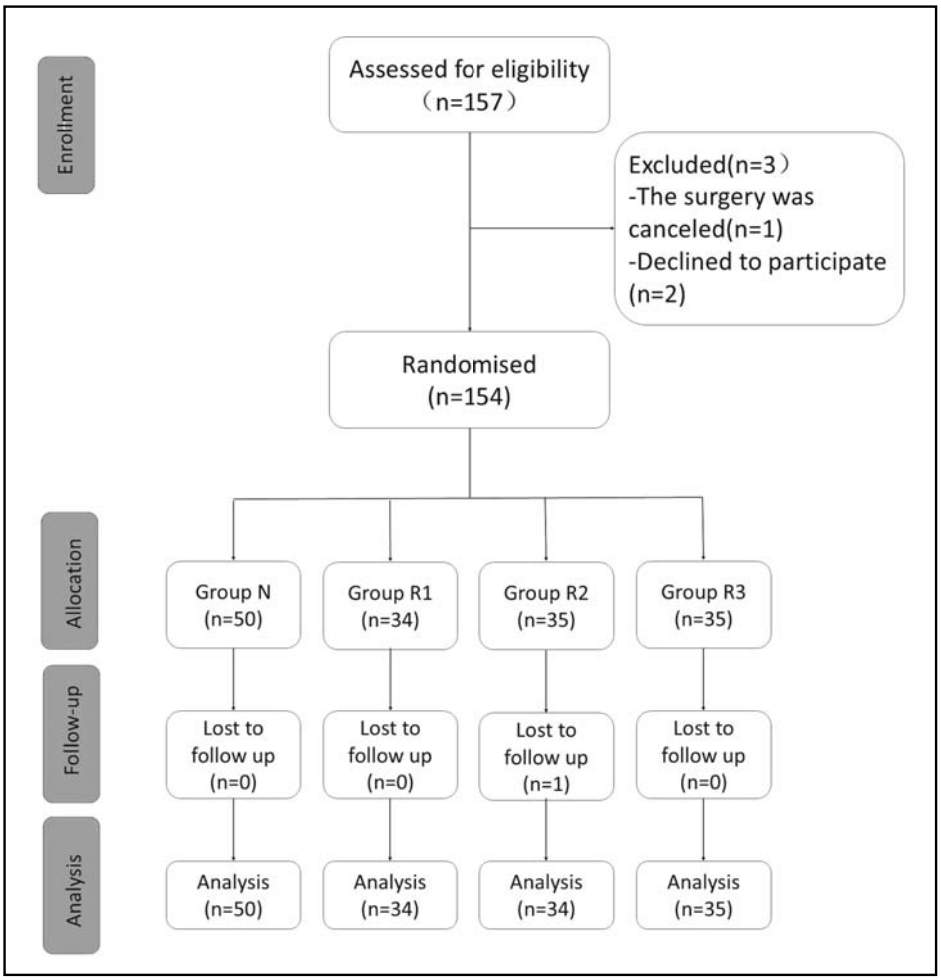

Fig. 1. Consort flowchart

deeper sedation: 0–2 points represented deep sedation, 3–4 points indicated mild to moderate sedation, and 5 points denoted complete wakefulness. During surgery, the target sedation level was defined as MOAA/S ≤ 3 points.

2. 3D-CAM: the CAM is a screening tool that enables clinicians without specialized psychiatric training to identify POD in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria. Diagnosis is based on four features using the CAM algorithm: (1) acute onset or fluctuating course of symptoms, (2) impaired attention, (3) incoherent thinking, and (4) altered level of consciousness. The 3D-CAM, an optimized version of the CAM, consists of 22 items and was used in this study to assess POD. Delirium was diagnosed if criteria 1 and 2, together with either 3 or 4, were present. A trained evaluator blinded to group allocation performed 3D CAM assessments twice daily (08:00 and 16:00) on postoperative days 1, 2, 3, 5, and 7. A diagnosis of POD was confirmed if diagnostic criteria were met at any assessment time point.
3. Stress indicators: At operating room entry and exit, 5 ml of peripheral venous blood was collected under fasting conditions. After standing and centrifugation, the supernatant was obtained. Cortisol and NE levels were measured using the enzyme-linked immunosorbent assay method.

Statistical methods

SPSS 27.0 software was used for data processing and analysis.

Normally distributed data are presented as mean ± standard deviation, and intergroup comparisons were conducted using one-way analysis of variance, followed by the least significant difference *t* test for pairwise comparisons. Non-normally distributed data are expressed as median (interquartile range), with the Kruskal–Wallis H test applied for intergroup comparisons and the Dunn–Bonferroni method used for pairwise comparisons. Categorical variables are expressed as number of cases (%), with group comparisons performed using the chi-squared (χ^2) test or Fisher's exact test as appropriate. All pairwise comparisons were corrected for the α level using the Bonferroni method ($\alpha' = 0.017$). A p-value < 0.05 was considered statistically significant.

Tab. 1. Baseline demographic and perioperative characteristics of older adults undergoing hip arthroplasty under neuraxial anesthesia in the saline control (N) and remimazolam groups (R1, R2, R3)

Indicators	N group (n = 50)	R1 group (n = 34)	R2 group (n = 34)	R3 group (n = 35)	*p*-value
Sex (male/female)	24/26	18/16	17/17	18/17	0.814
Age (years)	68.1±2.8	68.1±2.6	68.5±3.1	68.4±2.9	0.678
BMI(kg/m^2)	22.8±3.2	22.2±2.9	23.5±3.5	23.9±3.4	0.316
ASA(II/III)	41/9	32/2	32/2	34/1	0.442
Preoperative comorbidities					
Diabetes mellitus	11	5	0	4	0.724
Hypertension	35	25	26	25	0.892
Coronary heart disease	6	1	1	2	0.537
History of cerebral infarction	2	1	1	0	0.642
Others	1	1	2	0	0.282
Duration of surgery (min)	77.3±18.2	74.5±15.1	76.9±15.7	76.2±17.6	0.195
Duration of anesthesia (min)	126.8±18.1	120.4±12.9	125.2±13.8	123.5±15.6	0.167
Bleeding volume (ml)	255.8±130.3	270.6±107.6	272.4±109.0	265.7±113.2	0.579

Data are presented as mean ± standard deviation for continuous variables and number of cases (percentage) for categorical variables. BMI, body mass index; ASA, American Society of Anesthesiologists physical status. There were no statistically significant differences among groups for any baseline variable.

Tab. 2. Sedation success rate, number of rescue remimazolam administrations, and awakening time in the remimazolam groups

Groups	n	Sedation success rate (%)	Number of remediations (times)	Awakening time (min)
R1	34	33(97.06)	0(0~1)	6.41±0.77
R2	34	34(100)	0(0~1)	6.82±0.64
R3	35	32(91.43)	0(0~0)	8.16±0.93
p-value		0.187	0.949	<0.01

R1, low dose remimazolam 0.1 mg/(kg•h); R2, medium dose remimazolam 0.2 mg/(kg•h); R3, high dose remimazolam 0.3 mg/(kg•h). Sedation success rate is expressed as number of patients with successful sedation (percentage). The number of rescue sedative administrations (remediations) is presented as median (interquartile range). Awakening time (time from discontinuation of remimazolam infusion to MOAA/S score = 5) is presented as mean ± standard deviation.

RESULTS

A total of 157 patients were enrolled and randomized. Of these, 2 declined participation, 1 canceled surgery on the day of the procedure, and 1 declined postoperative follow-up. The remaining 153 patients were included in the final analysis (Figure 1). Demographic and baseline characteristics were comparable among the groups (Table 1).

Primary outcome: sedation effect

In the R1 group, sedation with remimazolam tosylate was discontinued in one participant due to uncorrectable hypotension. Sedation was successfully achieved in all participants in the R2 group. In the R3 group, sedation failure occurred in one participant because the rescue dose exceeded the loading dose while the MOAA/S score remained ≥ 4 points; additionally, sedation was discontinued in two participants due to uncorrectable hypotension. The final sedation success rates for the R1, R2, and R3 groups were 97.06%, 100%, and 91.43%, respectively, and Fisher's exact test did not detect a statistically significant difference in success rates among the groups ($p > 0.05$, Table 2).

No significant differences were observed in the number of rescue sedative administrations among the R1, R2, and R3 groups ($p > 0.05$, Table 2). MOAA/S scores did not differ significantly between groups at baseline (T0), at fixation of the anesthesia plane (T1), or at initiation of drug infusion (T2) (Table 3). Compared with T0, MOAA/S scores were significantly lower at T2, 15 minutes after infusion (T3), 30 minutes after infusion (T4), 1 hour after infusion (T5), and at the end of the operation (T6) in all three groups (Table 3).

At T3, MOAA/S scores in the R3 group were significantly lower than those in the R1 and R2 groups

Tab. 3. Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores at predefined intraoperative timepoints in the remimazolam groups

Groups	n	Prior to anesthesia (T0)	When the anesthesia plane is fixed (T1)	After sedation				
				When drug pumping began (T2)	When the drug is pumped for 15 minutes (T3)	When the drug is pumped for 30 minutes (T4)	When the drug is pumped for 1 hour (T5)	At the end of the operation (T6)
R1	34	5.0(5.0~5.0)	5.0(5.0~5.0)	3.0* (2.0~3.0)	3.0* (3.0~3.0)	3.0* (2.5~3.0)	4.0* (3.0~4.0)	4.0* (3.0~4.0)
R2	35	5.0(5.0~5.0)	5.0(5.0~5.0)	3.0* (2.0~3.0)	3.0* (2.0~3.0)	2.5* (2.0~3.0)	3.0*a (2.0~3.0)	3.0*a (3.0~3.0)
R3	35	5.0(5.0~5.0)	5.0(5.0~5.0)	3.0*ab(2.25~3.0)	2.0*ab (2.0~2.0)	2.0*ab (1.0~2.0)	2.0*ab (1.0~2.0)	2.0*ab (1.0~2.0)

Values are presented as median (interquartile range). R1, low dose remimazolam 0.1 mg/(kg•h); R2, medium dose remimazolam 0.2 mg/(kg•h); R3, high dose remimazolam 0.3 mg/(kg•h). Timepoints: T0, prior to anesthesia; T1, after fixation of the neuraxial anesthesia plane; T2, initiation of remimazolam infusion; T3, 15 minutes after infusion; T4, 30 minutes after infusion; T5, 1 hour after infusion; T6, end of operation. The MOAA/S scale ranges from 0 to 5, with lower scores indicating deeper sedation (0–2 deep sedation, 3–4 mild to moderate sedation, 5 fully awake). $p < 0.05$ vs T0 within the same group; a $p < 0.017$ vs R1 at the same timepoint; b $p < 0.017$ vs R2 at the same timepoint (Bonferroni adjusted α' = 0.017).

($p < 0.01$). Similar differences were observed at T4 ($p < 0.01$). At T5, scores in the R3 group were significantly lower than those in both the R1 and R2 groups ($p < 0.01$), and scores in the R2 group were significantly lower than those in the R1 group ($p < 0.01$). At T6, MOAA/S scores in the R3 group were again significantly lower than those in the R1 and R2 groups ($p < 0.01$), while scores in the R2 group were significantly lower than those in the R1 group ($p < 0.01$, Table 3).

The R2 and R3 groups largely maintained the target sedation depth (MOAA/S ≤3) from initiation of infusion (T2) to the end of surgery (T6), whereas the R1 group showed higher MOAA/S scores at T5 and T6, indicating comparatively lighter sedation in the later stages of the operation (Table 3). Awakening time did not differ significantly between the R1 and R2 groups (6.41 ± 0.77 min vs 6.82 ± 0.64 min, $p = 0.123$), whereas awakening time in the R3 group was significantly longer than in both R1 and R2 (8.16 ± 0.93 min, $p < 0.01$ for both comparisons; Table 2)."

Secondary outcome: incidence of postoperative delirium

The overall incidence of POD was low across all groups (2.86–6.00%), and no statistically significant differences were observed among the saline and remimazolam groups (R1, R2, R3; $p = 0.922$; Table 4). No statistically significant differences were found in time to onset between groups (log-rank $\chi^2 = 0.51$, $p = 0.916$; Table 4). Compared with the N group, the R1, R2, and R3 groups did not demonstrate significant differences in POD (Table 5). Pairwise comparisons, corrected by the Bonferroni method indicated no significant differences between any two groups.

Comparison of stress indicators

There was no significant difference in Cor and NE concentrations among the N, R1, R2, and R3 groups at operating room entry (Cor: $p = 0.889$; NE: $p = 0.373$). In the R1, R2, and R3 groups, cortisol and norepinephrine concentrations at operating room exit were numerically lower than at entry, but within-group changes did not reach statistical significance, whereas exit concentrations were significantly lower in all remimazolam

Tab. 4. Occurrence of postoperative delirium (POD) in the saline control and remimazolam groups

Groups	n	Day 1 after surgery (n)	Day 2 after surgery (n)	Day 3 after surgery (n)	Day 5 after surgery (n)	Day 7 after surgery (n)	Incidence of POD [n (%)]
R1	34	0	1	0	0	0	1(2.94)
R2	34	1	1	0	0	0	2(5.88)
R3	35	1	0	0	0	0	1(2.86)
N	50	2	1	0	0	0	3(6.00)
p-value		-	-	-	-	-	0.922

N, saline control group; R1, low dose remimazolam 0.1 mg/(kg•h); R2, medium dose remimazolam 0.2 mg/(kg•h); R3, high dose remimazolam 0.3 mg/(kg•h). POD was assessed using the 3D Confusion Assessment Method (3D CAM) twice daily on postoperative days 1, 2, 3, 5, and 7. Data are presented as number of patients with POD on each day and overall incidence (number of patients with POD, percentage).

groups than in the saline group (Table 6). In contrast, at operating room exit, cortisol and norepinephrine concentrations were significantly lower in all remimazolam groups than in the saline group ($p < 0.05$). In the N group, no significant differences were identified between entry and exit values (Cor: $p = 0.899$; NE: $p = 0.236$). Furthermore, no significant differences were found in exit concentrations among the R1, R2, and R3 groups (Cor: $p = 0.800$; NE: $p = 0.291$, Table 6).

Comparison of the incidence of adverse reactions and medications

Compared with the N group, the R1, R2, and R3 groups did not demonstrate significant increases in the use of ephedrine ($p = 0.259$), atropine ($p = 0.642$), or nicardipine ($p = 0.558$). No significant increases were observed in the incidence of hypoxemia ($p = 0.142$) or nausea and vomiting ($p = 0.642$). Within-group analysis indicated that the use of ephedrine (14.28%) and the incidence of hypoxemia (8.57%) were numerically higher in the R3 group; however, these differences did not reach statistical significance (Table 7).

Tab. 5. Odds ratios for postoperative delirium in remimazolam groups compared with the saline control group

Groups	OR value	95%CI	*p* value
R1	0.47	0.04~5.43	0.542
R2	0.97	0.13~7.2	0.976
R3	0.46	0.04~5.34	0.532

N, saline control group (reference); R1, low dose remimazolam 0.1 mg/(kg•h); R2, medium dose remimazolam 0.2 mg/(kg•h); R3, high dose remimazolam 0.3 mg/(kg•h). OR, odds ratio; CI, confidence interval. POD was defined by 3D CAM criteria at any assessment within the first 7 postoperative days.

DISCUSSION

Older adults generally exhibit reduced tolerance to surgery and anesthesia and are at increased risk of anesthesia-related complications due to diminished organ function, decreased compensatory capacity, and frequent comorbidities, which place higher demands on perioperative anesthesia management (Bantie *et al.* 2020; Pu & Sun, 2019). Consequently, the choice of anesthetic agents is particularly critical in this population (Shi *et al.* 2024). Remimazolam tosylate, a new ultra–short-acting water-soluble benzodiazepine derivative with distinctive pharmacodynamic and pharmacokinetic properties, has been widely used to maintain sedation in short procedures such as gastrointestinal endoscopy, hysteroscopy, and fiberoptic bronchoscopy (Zhang *et al.* 2022; Zhang *et al.* 2021). This agent exerts minimal effects on circulatory and respiratory function, and its action can be rapidly reversed with

Tab. 6. Plasma cortisol (Cor) and norepinephrine (NE) concentrations at operating room entry and exit in the saline control and remimazolam groups

Groups	n	Cor (ng/mL)		NE (nmol/L)	
		Entering the operating room	Exiting the operating room	Entering the operating room	Exiting the operating room
N	50	205.80±7.10	208.22±6.80	2.04±0.26	2.19±0.30
R1	34	205.21±9.80	201.51±8.11	1.94±0.28	1.73±0.25
R2	34	205.60±8.23	202.10±7.50	1.99±0.31	1.78±0.26
R3	35	206.32±7.10	203.62±8.92	2.03±0.29	1.92±0.24

Data are presented as mean ± standard deviation. N, saline control group; R1, low dose remimazolam 0.1 mg/(kg•h); R2, medium dose remimazolam 0.2 mg/(kg•h); R3, high dose remimazolam 0.3 mg/(kg•h). Cortisol is expressed in ng/mL and norepinephrine in nmol/L.

Tab. 7. Incidence of intraoperative adverse events and use of vasoactive medications in the saline control and remimazolam groups

Events/Medications	N group (n = 50)	R1 group (n = 34)	R2 group (n = 34)	R3 group (n = 35)	*p*-value
Ephedrine	6(12.00)	4(11.76)	3(8.82)	5(14.28)	0.976
Atropine	3(6.00)	1(2.94)	0(0.00)	1(2.86)	0.612
Nicardipine	2(4.00)	0(0.00)	1(2.94)	0(0.00)	0.482
Hypoxemia	0(0.00)	1(2.94)	1(2.94)	3(8.57)	0.142
Nausea and vomiting	1(2.00)	1(2.94)	0(0.00)	1(2.86)	0.849

N, saline control group; R1, low dose remimazolam 0.1 mg/(kg•h); R2, medium dose remimazolam 0.2 mg/(kg•h); R3, high dose remimazolam 0.3 mg/(kg•h). Data are presented as number of patients (percentage). Hypotension was defined as systolic blood pressure <90 mmHg or a mean arterial pressure decrease >25% from baseline and treated with ephedrine; hypertension as systolic blood pressure >120% of baseline and treated with nicardipine; bradycardia as heart rate <45 beats/min and treated with atropine; hypoxemia as peripheral oxygen saturation (SpO_2) <90%.

flumazenil, enhancing its suitability for older adults (Nakayama *et al.* 2021). However, although the use of remimazolam tosylate in older adult patients has been frequently reported, the optimal sedation dose during hip arthroplasty in this population has not been clearly established.

From previous studies and recommendations in the drug insert, a titration dosing regimen was selected for induction, and three maintenance dose groups (low, medium, and high) were established to determine the optimal sedation dose (Doi *et al.* 2020). The final success rates in the three groups were 97.06%, 100%, and 91.43%, respectively, which are consistent with findings from earlier clinical studies (Zhao *et al.* 2022). The maintenance doses applied in this study [0.1, 0.2, and 0.3 mg/(kg•h)] aligned with regimens reported in previous work and, in this cohort, 0.2 mg/(kg•h) provided the best balance of stable target range sedation, high success rate (100%), and relatively rapid recovery among the doses tested (Wang *et al.* 2025).

In the low-dose group (R1 group), sedation was discontinued in one participant due to uncorrectable hypotension. In the high-dose group (R3 group), sedation failure occurred in one participant because the rescue dose exceeded the loading dose while the MOAA/S score remained ≥ 4 points, and sedation was discontinued in two additional participants due to uncorrectable hypotension. All three patients with hypotension returned to normal levels following active treatment without any adverse event. These patients all had a history of hypertension; two were on long-term treatment with angiotensin-converting enzyme inhibitors, and one was receiving long-term therapy with a reserpine-containing antihypertensive agent. The intraoperative occurrence of hypotension may have been associated with the prolonged use of these medications.

The incidences of hypoxemia (8.57%) and hypotension requiring ephedrine correction (14.28%) were higher in the R3 group; however, the differences did not reach statistical significance compared with the N, R1, and R2 groups ($p > 0.05$). These findings indicate that, at the tested doses, continuous intraoperative sedation with remimazolam was generally well tolerated and was not associated with statistically significant increases in vasopressor use, bradycardia requiring atropine, hypoxemia, or nausea and vomiting compared with saline (Chen *et al.* 2020).

With regard to the intraoperative sedation effect, relevant literature on remimazolam tosylate was reviewed, and studies using the bispectral index (BIS) to assess anesthetic depth were identified. However, evidence indicates that BIS is more appropriate for monitoring sedation with propofol (Zhao *et al.* 2023). In benzodiazepine-based sedation, BIS values tend to remain higher and may be influenced by the concomitant use of other anesthetic agents (Ibrahim *et al.* 2001). Based on prior clinical studies, the MOAA/S score is considered the most reliable indicator for assessing sedation depth; therefore, MOAA/S scaling was selected for sedation assessment in this study (Bae *et al.* 2024).

The findings demonstrated that the low dose group (R1) was prone to insufficient sedation during the later stages of surgery (T5–T6). In contrast, both the medium dose group (R2) and the high dose group (R3) achieved the target sedation depth (MOAA/S score ≤ 3 points), with R2 maintaining greater stability and MOAA/S scores consistently near 3 points throughout the procedure. Thus, the R2 group [0.2 mg/(kg•h)] showed better maintenance of target range sedation than the lower and higher dose groups.

Regarding awakening time, no significant difference was observed between the R1 and R2 groups, whereas the R3 group had a longer awakening time than both R1 and R2. Within the evaluated dosing range, 0.2 mg/(kg•h) therefore provided a favorable balance between adequate sedation depth and recovery time in older adults undergoing hip arthroplasty under neuraxial anesthesia, maintaining MOAA/S scores close to the target (≤ 3) from T2 to T6 with a 100% sedation success rate and awakening times comparable to the low dose group but shorter than the high dose group.

In this study, POD incidence was low and similar across the saline and remimazolam groups (2.86–6.00%; $p = 0.922$), and no dose dependent trend was observed. Given the small number of delirium events and the sample size, the study was not powered to detect modest differences in POD incidence between groups; accordingly, the absence of statistically significant differences should be interpreted as hypothesis generating rather than definitive evidence of a neutral effect (Picton *et al.* 2018; Helmes & Ostbye, 2015). Within this range, delirium incidence did not increase with higher remimazolam maintenance doses. The 3D-CAM was selected as the tool for POD assessment. CAM has been validated in large, high-quality studies involving more than 1000 patients, with a reported sensitivity of 94%, specificity of 89%, and high inter-rater reliability (Inouye *et al.* 1990; Wong *et al.* 2010; Wei *et al.* 2008). However, given that evaluators in this study did not have formal psychiatric training, the clinical operability and reproducibility of CAM may be limited, with variability in interpretation and implementation. For this reason, the 3D-CAM was adopted. This tool preserves the essential features of CAM while simplifying the evaluation process, requiring an average of approximately 3 minutes to complete, and has demonstrated sensitivity of 92% and specificity of 95% in clinical validation (Olbert *et al.* 2019; Ramaswamy, 2023).

Plasma Cor and NE concentrations are recognized indicators of stress response (Plaschke *et al.* 2010; Mu *et al.* 2013). In this study, patients who received remimazolam tosylate for sedation had significantly lower postoperative Cor and NE levels at operating room exit compared with those who did not receive

remimazolam. Findings from Zhang *et al.* (2022) similarly showed that, compared with propofol, remimazolam tosylate for anesthesia induction and maintenance in older adults undergoing hip arthroplasty maintained intraoperative circulatory stability, reduced intraoperative stress responses, and decreased postoperative plasma cortisol concentrations, consistent with the present results. The observed reduction in Cor and NE concentrations at operating room exit in the remimazolam groups compared with saline may reflect attenuation of perioperative stress responses. However, because inflammatory mediators and other mechanistic markers were not measured and within group changes from entry to exit did not reach statistical significance in individual remimazolam groups, the underlying mechanisms remain speculative (Liu & Xiong, 2022).

In terms of safety, our analysis revealed no significant differences in safety outcomes between patients sedated with remimazolam and those in the normal saline control group ($p > 0.05$). This included comparable requirements for vasoactive drugs and similar incidences of postoperative adverse reactions, such as nausea and vomiting. Furthermore, the use rates of specific agents—atropine, ephedrine, and nicardipine—did not differ significantly across all four study groups ($p > 0.05$). Notably, although the high-dose remimazolam group (R3) exhibited numerically higher rates of ephedrine use (14.28%) and hypoxemia (8.57%), these differences were not statistically significant compared to the saline group ($p > 0.05$), and no additional adverse events were observed throughout the study. In this cohort, remimazolam provided effective sedation without a statistically significant increase in adverse events compared with saline, which is consistent with previous clinical observations (Liu *et al.* 2023). Interestingly, in a phase III trial comparing the efficacy and safety of remimazolam tosylate with propofol for colonoscopy, the incidence of adverse events was lower in the remimazolam group than in the propofol group (49.48% vs. 68.42%); however, adverse reactions such as dizziness (23.71%) and gait disturbances (26.29%) were reported (Chen *et al.* 2020). A likely explanation for this difference is that, unlike gastroscopy procedures in which patients are subject to varying degrees of mechanical trauma, sedation in this study was administered only after satisfactory analgesia had been achieved with neuraxial anesthesia. Consequently, lower doses of sedative medication were required, resulting in fewer adverse reactions.

This study had several important limitations. First, the generalizability of our findings is constrained by the study's limited sample size and single center setting, which may lead to selection bias and affect the precision of differential outcome analysis. In particular, the low absolute number of delirium events (1–3 cases per group) limits the statistical power to detect clinically relevant between group differences in POD incidence. To address these constraints, subsequent studies would benefit from a larger, multicenter design to enable more in-depth analysis. Second, the participants generally had good baseline status, well-controlled comorbidities, and long-term adherence to therapeutic regimens. Patients with obesity and severe comorbidities were excluded, which may limit the generalizability of these findings to broader and higher risk populations. Third, the infusion doses of remimazolam tosylate examined in this study represented several commonly used clinical regimens (0.1, 0.2, and 0.3 mg/(kg•h)). The 0.2 mg/(kg•h) regimen should therefore be interpreted as the most suitable dose within this tested range for older adults undergoing hip arthroplasty under neuraxial anesthesia in our setting, rather than as a definitive optimal dose for other procedures, populations, or dosing schemes. Further investigation is warranted. Fourth, the absence of full blinding in our study—particularly of the anesthesiologists assessing intraoperative sedation—could potentially lead to observer bias. Fifth, the risk of POD varies according to surgical type, while only hip arthroplasty was included in this study, thereby limiting generalizability. Sixth, the absence of objective monitoring tools such as the Bispectral Index (BIS) may have limited the precision of sedation depth assessment in this study. Finally, the evaluation was limited to short-term outcomes (within 7 days postoperatively) regarding the effects of remimazolam on postoperative cognitive function. Data on long-term cognitive outcomes remain unavailable, and future studies should address this gap.

Our findings are based on a study that aimed to explore the use of remimazolam as an adjunct sedative in older patients undergoing hip arthroplasty under neuraxial anesthesia. Future research could expand the sample size to further investigate the efficacy and safety of remimazolam across other surgical types beyond hip arthroplasty, in more diverse older populations (including those with obesity, severe comorbidities, or frailty who were excluded from this study), and with broader dosing regimens and monitoring strategies.

CONCLUSION

In conclusion, in older adults undergoing hip arthroplasty under neuraxial anesthesia, continuous infusion of remimazolam at 0.2 mg/(kg•h) provided effective and stable intraoperative sedation with a 100% success rate and relatively rapid recovery compared with 0.3 mg/(kg•h), while maintaining a similar sedation success to 0.1 mg/(kg•h). In this single center trial, remimazolam at 0.1–0.3 mg/(kg•h) was not associated with an increased observed incidence of POD and was associated with lower cortisol and norepinephrine concentrations at operating room exit compared with saline, although within group changes in these stress markers did not reach statistical significance.

DECLARATIONS

Ethics approval and consent to participate

Approval for this study was obtained from the Ethics Committee of the Second Hospital of Shanxi Medical University (2025-XY-0079), and written informed consent was obtained from all patients or their family members. This study was conducted in accordance with the declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Availability of data and materials

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Authors' contributions

Conception and design of the research: Zhi-Cong Ma, Tu-Ping Li, Yan-Qi Hou
Acquisition of data: Yan-Qi Hou
Analysis and interpretation of the data: Yan-Qi Hou, Tu-Ping Li
Statistical analysis: Yan-Qi Hou
Writing of the manuscript: Yan-Qi Hou
Critical revision of the manuscript for intellectual content: Tu-Ping Li, Zhi-Cong Ma
All authors read and approved the final draft.

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