

Efficacy and Safety of Remimazolam Besylate versus Dexmedetomidine for Sedation in Non-Intubated Older Patients with Agitated Delirium After Orthopedic Surgery: A Randomized Controlled Trial

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Purpose: The purpose of the present study was to investigate the efficacy and safety of remimazolam besylate compared with dexmedetomidine for the relief of agitated delirium in non-intubated older patients after orthopedic surgery.

Patients and methods: Seventy-five patients were randomly divided into two groups. Patients assigned to the remimazolam group received a loading dose of 0.075 mg/kg remimazolam besylate over 1 minute, followed by a continuous infusion of 0.1 to 0.3 mg/kg/h. Subjects randomized to the dexmedetomidine group received a loading infusion of 0.5 µg/kg dexmedetomidine over 10 minutes, followed by a maintenance dose of 0.2 to 0.7 µg/kg/h. Meanwhile, RASS score-guided dose titration was followed. To assess the efficacy of the study drugs in terms of time to resolution of agitation, time to first achievement of target sedation, percentage of time within the target sedation range, and time to delirium resolution. Safety of the sedatives was evaluated by adverse events during hospitalization.

Results: Time to resolution of agitation did not differ between the two groups. The time to first achievement of target sedation was 19.0 (9.5 to 31.0) minutes for remimazolam besylate vs 43.5 (15.0 to 142.5) minutes for dexmedetomidine ($P < 0.001$). Percentage of time within the target sedation range was 77.8% for remimazolam besylate-treated patients and 67.4% for dexmedetomidine-treated patients ($P = 0.001$). Patients in the remimazolam group had longer time to delirium resolution (29.5 [21.3 to 32.5] hours) than those in the dexmedetomidine group (22.8 [18.9 to 28.5] hours) ($P = 0.042$). Patients sedated with remimazolam besylate had more over-sedation ($P = 0.036$) but less hypotension ($P = 0.007$).

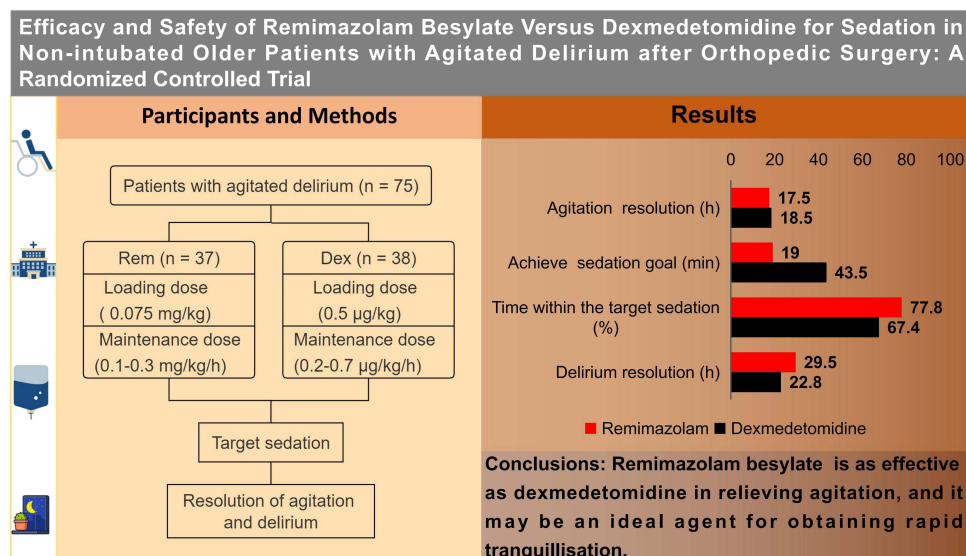
Conclusion: Compared with dexmedetomidine, remimazolam besylate was equally effective in relieving agitation, and resulted in earlier achievement of sedation goal and more controllable sedation. Remimazolam may be an ideal agent for obtaining rapid tranquillisation.

Keywords: remimazolam besylate, dexmedetomidine, older adult, orthopedics, agitation, delirium

Introduction

Postoperative delirium is a common and serious problem in older patients following orthopedic surgery, with an incidence of 24.0% to 55.9% in hip fracture patients and 12.5% to 24.3% in geriatric patients undergoing spine surgery.¹⁻³ The hyperactive delirium is the most common subtype and is often characterized by agitation.^{3,4} Uncooperative agitation is dangerous in orthopedic procedure that requires temporary postoperative immobilization because of the risk of self-inflicted physical damage such as prosthetic dislocation. It can also cause great distress to caregivers, healthcare professionals, and patients themselves.⁴ In addition to patients experiencing mechanical ventilation with endotracheal intubation, agitation is not uncommon in non-intubated patients. Sedation management in such populations is more challenging because of the absence of a secure airway.⁵

Graphical Abstract



To date, studies on the management of sedation in non-intubated agitated patients are rare. Although haloperidol and some atypical antipsychotics (olanzapine, risperidone, etc) are recommended by guidelines, relevant studies have shown conflicting results.⁵⁻⁷ A study in non-intubated patients with agitated delirium showed that the failure rate for haloperidol was 43%, whereas dexmedetomidine could be used as a rescue agent for hyperactive delirium refractory to haloperidol.⁶ Nonetheless, dexmedetomidine may not be applicable for older patients with uncooperative or even dangerous agitation. Lower doses of dexmedetomidine are usually ineffective for rapid tranquilization, while adverse cardiovascular effects induced by a higher starting dose are inevitable, especially in fragile patients. Meta-analysis showed that the incidence of bradycardia, hypotension and hypoxemia in elderly patients treated with dexmedetomidine was 23.1%, 36.3%, and 10.4%, respectively.⁸ Among the benzodiazepines, midazolam and lorazepam are considered to be the preferred drugs for rapid tranquilization in patients with acute agitation or excited delirium due to their rapid onset of action and short half-life.^{4,9} As a new ultra-short-acting benzodiazepine, remimazolam tosylate has been approved for procedural sedation in China.¹⁰ Remimazolam has faster onset of action and higher safety profile, does not rely on specific organ to be metabolized, and can be rapid removal even after prolonged infusion.^{11,12} During procedural sedation, the incidence of hypotension and respiratory depression in patients sedated with remimazolam was 13.0% to 23.7% and 1.1% to 3.1%, respectively, which were significantly lower than those in the propofol sedation group.^{13,14} In addition, flumazenil reverses the effects of remimazolam in the event of adverse events, an advantage not available in non-benzodiazepines.¹⁰ Based on these unique pharmacological effects, we hypothesized that remimazolam should be a reasonable option for relieving agitated delirium in non-intubated older patients. The objective of this randomized clinical trial was to evaluate the efficacy and safety of remimazolam besylate compared with dexmedetomidine for the relief of agitated delirium in non-intubated older patients after orthopedic surgery.

Methods

Study Design

This single-center, prospective, randomized, single-blind, controlled clinical trial was conducted in the Geriatric Orthopedic Center of Sichuan Provincial Orthopedic Hospital from September 2020 to November 2021. In our institution, the process of perioperative management for older patients follows established standards.¹⁵

Ethics Approval and Consent to Participate

All procedures performed in this study conformed to the ethical guidelines of the Declaration of Helsinki and were approved by the Ethics Committee of Sichuan Provincial Orthopedic Hospital (KY-2020-031-01). For research purpose, participants recruited for the study were experiencing agitation and had lost their normal cognitive, behavioral abilities. Therefore, we obtained informed consent for participation from the patient's legal representative. Given the risk of sedation in non-intubated older patients, the study must be conducted in an intensive care unit (ICU) setting. In emergency situations (presence of risks of acute agitation-related adverse events such as unexpected tube removal, prosthetic hip dislocation and other self-inflicted physical damages), patients could be transferred to ICU with the verbal consent of their representatives. However, written informed consent must be obtained before administration of study medication. Patients or their representatives can withdraw the consent at any stage. The clinical trial was pre-registered at the Chinese Clinical Trial Registry on August 21, 2020, with the unique identifier: ChiCTR2000036101.

Enrollment Criteria

Older patients (aged ≥ 70 years) after orthopedic surgery were eligible for the study if they developed agitated delirium. The following criteria should be met for the determination of agitated delirium: 1) Confusion Assessment Method for the ICU (CAM-ICU) results showed presence of delirium with a Richmond Agitation-Sedation Scale (RASS) score ≥ 2 ¹⁶ and 2) Motor Activity Assessment Scale (MAAS) score ≥ 5 .¹⁷ Patients were excluded if they 1) developed acute agitation before or within 4 hours of anesthesia resuscitation (successful removal of an artificial airway was regarded as a sign of recovery from anesthesia); 2) were already receiving dexmedetomidine or other sedatives; 3) had grade C or higher of Stages of Heart Failure, and second-degree or higher of atrioventricular block; 4) had serious central nervous system disorders (craniocerebral trauma, acute stroke, progressive dementia); 5) had a history of mental disorders or alcohol dependence; 6) were unable to complete the relevant assessment due to language, hearing, and visual impairment; and 7) were allergic to the drugs used in the study.

Randomization and Blinding

To ensure the balance of the number of participants between the two groups, a blocked randomization was used. Block sizes were randomly set to 2, 4, and 6; participants in each block were determined according to their inclusion order number and randomly assigned 1:1 to receive sedation with remimazolam besylate or dexmedetomidine based on a randomization code generated by SPSS version 20.0. This clinical trial was a single-blinded study, because the sedation protocols were completely different between the two groups. The treating physician and bedside nurse performing the sedation protocols could not remain blind to the study group allocation. However, assessors of study outcomes were independent.

Study Drug Administration

Predetermination of Study Drug Dose

Subjects randomized to the dexmedetomidine group received a loading infusion of 0.5 $\mu\text{g/kg}$ dexmedetomidine {Yangtze River Pharmaceutical (Group) Co., Ltd. Jiangsu, China} over 10 minutes, followed by a maintenance dose of 0.2 to 0.7 $\mu\text{g/kg/h}$.⁶

A loading dose of 0.075 mg/kg for remimazolam besylate (Hengrui Pharmaceuticals Co., Ltd. Jiangsu, China) was predetermined in consideration of the poor sedation tolerance of the subjects.^{10,18,19} Due to the limited use of remimazolam in non-anesthetic settings, it was difficult to predetermine appropriate dose for sedation maintenance. A study in healthy Chinese volunteers recommended 1.0 mg/kg/h of remimazolam besylate as a maintenance dose for general anesthesia. During continuous infusion at this dose, the venous plasma concentration was maintained around 800 ng/mL with a bispectral index value of 40 to 60 (no response to noxious stimuli), and the bispectral index value approached 80 (respond to vocal commands) when the plasma concentration decreased to around 200 ng/mL.^{20,21} Based on the above findings, the maintenance dose of remimazolam besylate was tentatively predetermined to 0.1 to 0.3 mg/kg/h (nearly a quarter of the maintenance dose for general anesthesia) in the present study. To minimize the risk of oversedation, a dose titration guided by the RASS score was performed in the subsequent treatment.

Dose Titration of Study Drug

Study medications were titrated by the bedside nurse to achieve the targeted sedation range (RASS score of -2 to 0) according to the following protocol: 1) If $1 \leq \text{RASS score} \leq 2$ after continuous infusion of sedatives for more than 15 minutes, the doses of remimazolam besylate and dexmedetomidine were uptitrated with steps of 0.05 mg/kg/h and $0.1 \text{ } \mu\text{g/kg/h}$, respectively. The interval between each dose adjustment should be at least 15 minutes. 2) If the infusion doses of study medications reached the predetermined upper limit for more than 15 minutes and the RASS score remained at 3 or above, 0.5 to 1 mg/kg of propofol was temporarily administered as a sedation rescue under the supervision of the treating physician to prevent serious agitation-related adverse events. 3) If RASS score ≤ -3 during continuous infusion, the administration of sedatives was reduced or discontinued until patients returned to the acceptable sedation range.

Intermittent Awakening Protocol

To avoid the use of non-essential sedatives as much as possible and reduce the risk of bias from delirium assessment in patients receiving moderate sedation,²² we designed an intermittent awakening protocol with reference to the “daily awakening”. After the sedation goal was first reached, continuous infusion of sedatives was interrupted every 8 hours unless the patient was in agitation at this stage. If agitation recurred within 1 hour after interruption of sedation, sedatives were re-administered, as previously described in protocol. If the MAAS score remained at 2 to 4 after 1 hour, the agitation was considered resolved and the sedation therapy was completely discontinued. Therefore, 8 hours of continuous sedation and one interruption of sedation were considered as a complete “observation period” in this study.

Safety Measures

Oversedation in the absence of a safe airway can have catastrophic consequences.⁵ In this study, subjects were confined to the ICU setting to receive the study drugs. All patients received continuous monitoring of respiratory rate (RR), heart rate (HR), peripheral capillary oxygen saturation (SpO_2), noninvasive blood pressure (NIBP), and oxygen therapy (3 to 5 L/min oxygen administered with nasal cannula) prior to randomization. To ensure airway safety, the treating physician involved must be an intensivist with the ability to manage the airway (chin lifting, ventilation assistance, endotracheal intubation, etc). In addition to the bedside nurse, the treating physician should observe the subject's responsiveness at the bedside for at least 15 minutes after the loading dose of the study drug or propofol was administered. Arterial blood gas analysis was performed before and 1 hour after sedation. In the case of hypoxemia, hypotension, and bradycardia, emergency measures included chin lifting, increasing the fraction of inspired oxygen, assisted ventilation via mask, fluid or vasoactive drugs therapy.

Pain Management and Subsequent Assessments

Postoperative pain management included patient-controlled analgesia (PCA) and intravenous administration of parecoxib sodium 40 mg every 12 hours and/or tramadol hydrochloride 50 to 100 mg every 6 to 8 hours as needed. Other sedatives or analgesics are not allowed during the study. A Faces Pain Scale-Revised score ≤ 4 is the goal of pain management.²³ Agitation and delirium were assessed every 6 hours during the first 24 hours following complete discontinuation of sedatives, and every 12 to 24 hours until discharge. If abnormal consciousness or behavior was reported by the caregiver or nurse, the immediate assessment and corresponding treatment were performed.

Outcomes

The primary outcome was time to resolution of agitation (the first achievement of a MAAS score of 2 to 4 after 1 hour of sedation interruption).²⁴ Secondary outcomes contained time to first achievement of target sedation (RASS score of -2 to 0), proportion achieving target sedation within 1 hour, percentage of time within the target sedation range during treatment with study medications,²⁵ time to delirium resolution (the first CAM-ICU results indicated absence of delirium at least 1 hour after interruption of sedation), proportion of recurrent delirium or agitation (after the first resolution of delirium or agitation, the CAM-ICU and MAAS results showed a recurrence of delirium or agitation), length of hospital stay. Considering the different administration time of loading dose of two study drugs, all time-to-event data were calculated from the end of loading dose. Adverse events included proportion of oversedation, hypoxemia, hypotension, and bradycardia (including cases with

combined propofol use), incidence of pulmonary infection and deep venous thrombosis (excluding those occurring prior to enrollment). A RASS score ≤ -3 was considered oversedation, as it would be an unacceptable depth of sedation. Hypoxemia referred to $\text{SpO}_2 < 90\%$ or more than 10% reduction from baseline, hypotension was defined as systolic blood pressure (SBP) < 80 mmHg or more than 30% decrease from baseline, the definition of bradycardia was $\text{HR} < 50$ beats per minute or more than 30% decrease from baseline. SpO_2 , SBP and RR measured at calm after admission were considered as baseline value. Diagnosis of pulmonary infection was based on clinical manifestations, chest CT scan, and aetiological tests, and deep venous thrombosis was identified by a Doppler ultrasound scan of the lower legs. We also recorded vital signs and arterial blood gas analysis parameters before sedation initiation and 1 hour after sedation implementation.

Statistical Analysis

Based on previous literature and our pilot study, the mean \pm standard deviation of the time to resolution of agitation in these agitated patients was assumed to be 18.0 ± 6.0 hours.^{6,24} Using a two-tailed hypothesis at an α level of 0.05, an estimated sample size of 72 cases provided 80% power in detecting a 4.5-hour difference of resolution of agitation (estimation based on our pilot study). The above sample size calculations contained an inflation rate of 15% to account for the possibility that time to resolution of agitation would not be normally distributed. Considering also a dropout rate of 10%, we included a total of 80 patients.

Continuous variables were expressed as mean and standard deviation or median and interquartile range (IQR), and two independent sample *t*-test or Mann–Whitney *U*-test was used to assess the difference between the two groups as appropriate. Categorical data were presented as frequency and percentage and compared using χ^2 or Fisher's exact tests. The differences in primary and secondary outcome between the two groups and their 95% confidence intervals (CIs) were calculated and reported. Time-to-event data were calculated using Log rank tests, and Kaplan–Meier curves were plotted. Statistical tests were two-sided, and a probability $P < 0.05$ was considered statistically significant. All statistical evaluations were conducted using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Results

From September 1, 2020 to November 30, 2021, 80 patients were randomly assigned to two groups. However, three patients allocated to the remimazolam besylate group withdrew consent and two patients were incorrectly enrolled in the dexmedetomidine group (dexmedetomidine was already included in the PCA pump for postoperative analgesia), leaving data from 37 patients in the remimazolam besylate group and 38 patients in the dexmedetomidine group for final statistical analysis (Figure 1). Baseline characteristics of the study participants are presented in Table 1. The patients who received hip arthroplasty accounted for 46.7% (35/75) of the final enrolments, and the rest received various types of internal fixation. All patients underwent surgery under general anesthesia with laryngeal mask or endotracheal intubation. The duration of study drug treatment was 16.0 hours (IQR, 8.5 to 17.3) in the remimazolam besylate group and 17.0 hours (IQR, 11.6 to 19.1) in the dexmedetomidine group, respectively. The mean maintenance infusion dose was 0.12 mg/kg/h (IQR, 0.11 to 0.15) for remimazolam besylate and 0.51 $\mu\text{g/kg/h}$ (IQR, 0.36 to 0.64) for dexmedetomidine. A total of six patients in the remimazolam besylate group had a mean maintenance infusion dose below the lower limit of the predetermined dose range. Propofol was used as an emergency sedative rescue in four patients (one in the remimazolam besylate group and three in the dexmedetomidine group).

Primary Outcome

There was no significant difference in the primary outcome of time to resolution of agitation (median, 17.5 hours [IQR, 9.5 to 18.3] in the remimazolam besylate group vs 18.5 hours [IQR, 13.9 to 21.4] in the dexmedetomidine group; median difference between groups, -1.5 hours [95% CI, -5 to 0]; $P = 0.721$). In 82.7% of the patients, agitation was resolved within two observation periods, while only 6.7% of the patients required more than three observation periods to resolve agitation. The distribution of resolution of agitation at each observation period did not differ between the two groups ($P = 0.770$) (Table 2, Figure 2A).

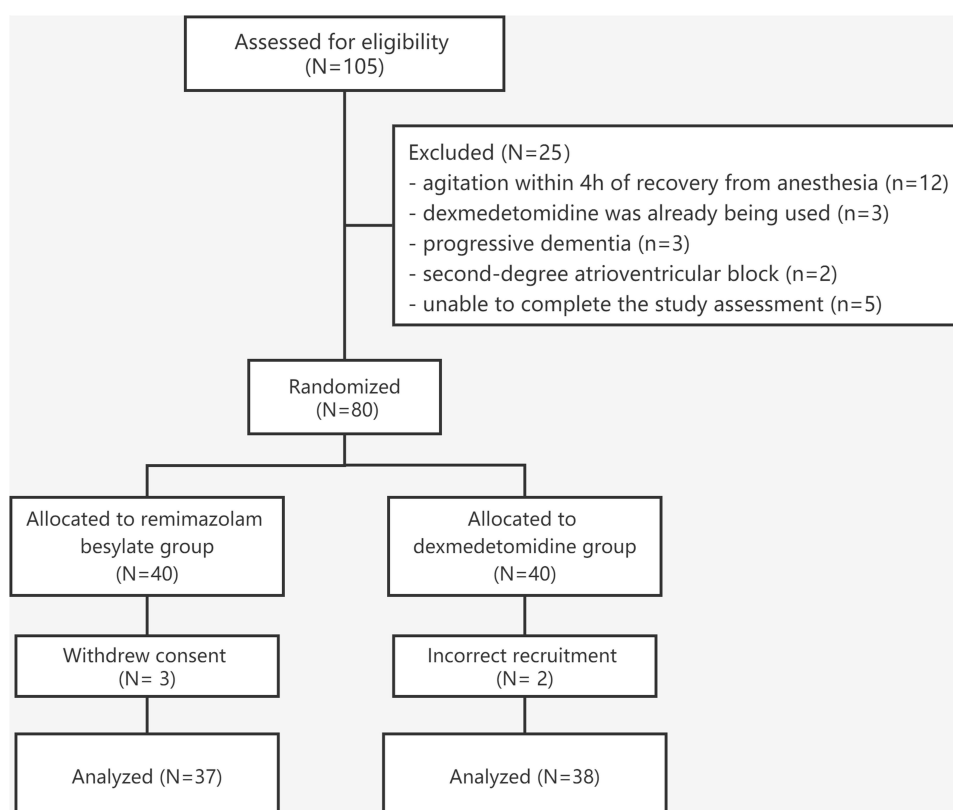


Figure 1 Flow chart of study participants.

Secondary Outcomes

The median time to first achievement of target sedation was 19.0 minutes (IQR, 9.5 to 31.0) for remimazolam besylate vs 43.5 minutes (IQR, 15.0 to 142.5) for dexmedetomidine (median difference between groups, -17.0 minutes [95% CI, -65.0 to -3.0]; $P < 0.001$). Correspondingly, there was a significant difference in the proportion achieving target sedation within 1 hour (89.2% in the remimazolam besylate group vs 55.3% in the dexmedetomidine group; difference, 33.9% [95% CI, 15.2% to 52.6%]; $P = 0.002$) (Table 2, Figure 2B). Percentage of time within the target sedation range was significantly different between the two groups (77.8% for remimazolam besylate-treated patients and 67.4% for dexmedetomidine-treated patients; difference, 11.1% [95% CI, 4.4% to 18.2%]; $P = 0.001$) (Table 2). Patients in the remimazolam besylate group had longer time to delirium resolution (median, 29.5 hours [IQR, 21.3 to 32.5]) than those in the dexmedetomidine group (median, 22.8 hours [IQR, 18.9 to 28.5]) (median difference between groups, 4.0 hours [95% CI, 0 to 8.5]; $P = 0.042$) (Table 2, Figure 2C). After 1 hour of sedation interruption, 27.0% of the patients in the remimazolam group and 63.2% of the patients in the dexmedetomidine group not only maintained a MAAS score of 2 to 4 but also achieved negative CAM-ICU results (difference between groups, -36.1% [95% CI, -57.1% to -15.2%]; $P = 0.002$). These patients were considered to have “simultaneous resolution of agitation and delirium”. The CAM-ICU results remained positive after the MAAS score reached the target in the rest of the subjects. There was no difference in the proportion of recurrent agitation or delirium between the two groups (Table 2). Post hoc analyses for the time to delirium resolution was performed in subgroups according to the observation period of the resolution of agitation. A total of 26 patients had resolution of agitation during the first observation period, and their time to delirium resolution was 21.0 hours (IQR, 15.3 to 22.3) in the remimazolam group ($n = 13$) and 21.5 hours (IQR, 9.5 to 24.3) in the dexmedetomidine group ($n = 13$) (difference, 0 hours [95% CI, -4 to 11.5]; $P = 0.920$). The remaining 49 patients were assigned to another subgroup whose agitation lasted for two or more observation periods. In this subgroup, time to delirium resolution was 30.0 hours (IQR, 27.6 to 39.8) in the remimazolam group ($n = 24$) and 26.0 hours (IQR, 19.0 to 30.5) in the dexmedetomidine group ($n = 25$) (difference, 6.5 hours [95% CI, 0.5 to 11.0]; $P = 0.029$).

Table 1 Baseline Characteristics of the Patients

Variable	Remimazolam Besylate (n = 37)	Dexmedetomidine (n = 38)	P-value
Age (years)	81.5 ± 7.5	82.3 ± 5.2	0.630
Number of males/females	17/20	12/26	0.240
Weight (kg)	56.2 ± 11.1	52.2 ± 10.4	0.113
Surgical site, n (%)			
Upper limb	3 (8.1)	4 (10.5)	0.787
Lower limb	29 (78.4)	26 (68.4)	
Spine	4 (10.8)	6 (15.8)	
Pelvis	1 (2.7)	2 (5.3)	
Comorbidities, n (%)			
Hypertension	12 (32.4)	16 (42.1)	0.476
Diabetes	7 (18.9)	12 (31.6)	0.289
Chronic heart disease	7 (18.9)	5 (13.2)	0.544
Chronic lung disease	4 (10.8)	6 (15.8)	0.736
Chronic central nervous system disease	8 (21.6)	11 (28.9)	0.597
Interval between anesthesia resuscitation and the onset of agitation (h)	8.0 (7.0 to 13.0)	11.0 (7.8 to 18.0)	0.219
RASS score prior to enrollment	2.0 (2.0 to 3.0)	2.0 (2.0 to 2.25)	0.578
Duration of agitation prior to enrollment (min)	25.0 (17.0 to 40.0)	35.0 (20.0 to 46.3)	0.211
Analgesia prior to enrollment, n (%)			
PCA ^a	31 (83.8)	30 (78.9)	0.768
Opioids use ^b	20 (54.1)	23 (60.5)	0.644
NSAIDS use	26 (70.3)	30 (78.9)	0.435
Tramadol use	6 (16.2)	4 (10.5)	0.516

Notes: ^aIncluding patient-controlled intravenous analgesia and patient-controlled nerve analgesia; ^bRefers to opioids included in the prescription of PCA.

Abbreviations: RASS, Richmond Agitation–Sedation Scale; PCA, patient-controlled analgesia; NSAIDS, nonsteroidal anti-inflammatory drugs.

Adverse Outcomes

All of the oversedation and hypoxemia occurred after administration of a loading dose rather than during continuous infusion. Of the 13 patients who developed oversedation, 7 had hypoxemia. Hypoxemia was gradually relieved after chin lifting in three cases of the remimazolam besylate group and one case of the dexmedetomidine group. The remaining three patients showed only a transient reduction in RR, and SpO₂ gradually rose after increasing the fraction of inspired oxygen. Patients randomized to the remimazolam besylate group had significantly more oversedation (27.0% vs 7.9% in the dexmedetomidine group; difference, 19.1% [95% CI, 2.4% to 35.8%]; *P* = 0.036). However, the incidence of hypoxemia was not different between the two groups. Fewer patients in the remimazolam besylate group experienced hypotension compared with the dexmedetomidine group (10.8% vs 39.5%, respectively; difference, −28.7% [95% CI, −47.2% to −10.2%]; *P* = 0.007) (Table 2). There was no difference in HR, RR, SpO₂, mean arterial pressure, partial

Table 2 Primary and Secondary Outcomes

Variable	Remimazolam Besylate (n = 37)	Dexmedetomidine (n = 38)	Difference Between Groups (95% CI)	P-value
Primary outcome				
Time to resolution of agitation ^a (h)	17.5 (9.5 to 18.3)	18.5 (13.9 to 21.4)	−1.5 (−5.0 to 0)	0.721
Proportion of agitation resolution in each observation period ^b , n (%)				
1st observation period	13 (35.1)	13 (34.2)	0.9 (−20.6 to 22.4)	0.770
2nd observation period	16 (43.2)	20 (52.6)	−9.4 (−31.9 to 13.1)	
3rd observation period	5 (13.5)	3 (7.9)	5.6 (−8.4 to 19.6)	
More than 3 observation periods	3 (8.1)	2 (5.3)	2.8 (−8.5 to 14.1)	
Secondary outcomes				
Time to first achievement of target sedation ^c (min)	19.0 (9.5 to 31.0)	43.5 (15.0 to 142.5)	−17.0 (−65.0 to −3.0)	< 0.001
Proportion achieving target sedation ^c within 1 hour, n (%)	33 (89.2)	21 (55.3)	33.9 (15.2 to 52.6)	0.002
Percentage of time within the target sedation range ^c (%)	77.8	67.4	11.1 (4.4 to 18.2)	0.001
Time to delirium resolution ^d (h)	29.5 (21.3 to 32.5)	22.8 (18.9 to 28.5)	4.0 (0 to 8.5)	0.042
MAAS and CAM–ICU results showed simultaneous resolution of agitation and delirium, n (%)	10 (27.0)	24 (63.2)	−36.1 (−57.1 to −15.2)	0.002
Proportion of recurrent delirium, n (%)	5 (13.5)	3 (7.9)	5.6 (−8.4 to 19.6)	0.480
Proportion of recurrent agitation, n (%)	2 (5.4)	1 (2.6)	2.8 (−6.1 to 11.7)	0.615
Length of hospital stay (d)	14.0 (11.0 to 18.0)	14.5 (12.0 to 20.3)	−1.0 (−4.0 to 1.0)	0.387
Adverse events				
Oversedation, n (%)	10 (27.0)	3 (7.9)	19.1 (2.4 to 35.8)	0.036
Hypoxemia, n (%)	5 (13.5)	2 (5.3)	8.2 (−4.9 to 21.3)	0.262
Hypotension, n (%)	4 (10.8)	15 (39.5)	−28.7 (−47.2 to −10.2)	0.007
Bradycardia, n (%)	1 (2.7)	5 (13.2)	−10.5 (−22.5 to 1.5)	0.200
Pulmonary infection ^e , n (%)	3 (8.1)	3 (7.9)	0.2 (−12.1 to 12.5)	1.000
Deep venous thrombosis ^e , n (%)	1 (2.7)	0	2.7 (−2.5 to 7.9)	0.493

Notes: ^aAssessed as MAAS score of 2 to 4 after 1 hour of sedation interruption; ^bOne observation period was defined as 8 hours of continuous sedation with a corresponding interruption of sedation; ^cAssessed as Richmond Agitation-Sedation Scale score of −2 to 0; ^dCAM-ICU results indicated absence of delirium at least 1 hour after interruption of sedation; ^eExcluding those occurring prior to enrollment.

Abbreviations: MAAS, Motor Activity Assessment Scale; CAM-ICU, Confusion Assessment Method for the ICU.

pressure of oxygen in arterial blood, and partial pressure of carbon dioxide in arterial blood between the two groups before and 1 hour after sedation (Table 3).

Discussion

In this randomized single-blind controlled clinical trial involving non-intubated older patients with agitated delirium after orthopedic surgery, the time to resolution of agitation as the primary outcome did not differ between the two groups. However, several secondary outcomes with significant differences were notable. Compared to dexmedetomidine, remimazolam besylate resulted in earlier achievement of target sedation and increased the percentage of time within

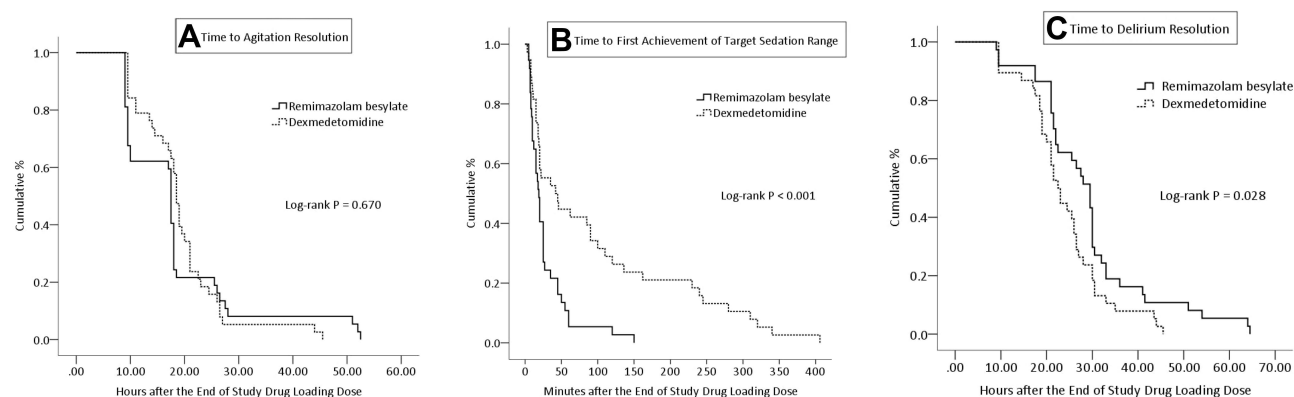


Figure 2 Kaplan–Meier curves for the efficacy of remimazolam besylate and dexmedetomidine. **(A)** Comparison of time to agitation resolution between the two groups; **(B)** Comparison of time to first achievement of target sedation range between the two groups; **(C)** Comparison of time to delirium resolution between the two groups.

the target sedation range, but delayed delirium resolution. A loading dose of remimazolam besylate induced more oversedation, whereas patients treated with dexmedetomidine experienced more hypotension.

In recent years, there have been numerous studies on pharmacological prevention and treatment for delirium, including antipsychotic drugs, dexmedetomidine, propofol, benzodiazepines.^{26–28} Evidence for the use of antipsychotic drugs in prophylaxis of delirium is insufficient, and most studies have shown no benefit of antipsychotics in reducing the duration or severity of delirium.^{29,30} And some adverse effects such as extrapyramidal symptoms and increasing the corrected QT interval need to be noticed.²⁶ Current evidence does not support the use of antipsychotics to treat or prevent

Table 3 Vital Signs and Arterial Blood Gas Analysis in Patients Treated with Remimazolam Besylate vs Dexmedetomidine

Variable	Remimazolam Besylate (n = 37)	Dexmedetomidine (n = 38)	Difference Between Groups (95% CI)	P-value
Before sedation				
HR (beats per minute)	83.0 (73.0 to 102.0)	88.0 (77.0 to 97.3)	−1.0 (−9.0 to 9.0)	0.886
MAP (mmHg)	93.8 ± 16.0	94.5 ± 10.6	−0.7 (−6.9 to 5.5)	0.824
RR (breaths per minute)	20.0 (18.5 to 24.5)	19.0 (18.0 to 22.3)	1.0 (−1.0 to 2.0)	0.331
SaO ₂ (%)	98.0 (97.0 to 99.0)	97.0 (96.0 to 98.0)	1.0 (0 to 1.0)	0.129
PaO ₂ (mmHg)	87.0 (75.5 to 100.0)	95.5 (86.5 to 112.0)	−9.0 (−18.0 to 0)	0.058
PaCO ₂ (mmHg)	39.0 ± 7.9	41.1 ± 5.6	−2.2 (−5.3 to 1.0)	0.176
After 1 hour of sedation				
HR (beats per minute)	79.0 (65.0 to 88.0)	71.0 (65.7 to 82.0)	5.0 (−2.0 to 11.0)	0.211
MAP (mmHg)	82.8 ± 14.3	77.8 ± 14.4	5.0 (−1.6 to 11.6)	0.136
RR (breaths per minute)	17.0 (16.0 to 20.0)	18.0 (17.0 to 19.0)	−1.0 (−2.0 to 0)	0.156
SaO ₂ (%)	98.0 (97.0 to 99.0)	98.0 (97.0 to 99.0)	0 (−1.0 to 0)	0.557
PaO ₂ (mmHg)	102.0 (80.0 to 121.0)	98.0 (85.8 to 119.0)	−0.5 (−12.0 to 12.0)	0.945
PaCO ₂ (mmHg)	43.1 ± 7.7	43.3 ± 5.5	−0.3 (−3.3 to 2.8)	0.866

Abbreviations: HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate; SaO₂, arterial oxygen saturation; PaO₂, partial pressure of oxygen in arterial blood; PaCO₂, partial pressure of carbon dioxide in arterial blood.

delirium in hospitalized older adults.^{30,31} Dexmedetomidine seems to exhibit distinct advantages and is recommended for clinical use because of its prophylactic and direct antidelirium effects.^{32–34} Given the potential for precipitating or worsening delirium, the application of benzodiazepines is only accepted in particular situations, such as abstinence from benzodiazepine themselves or alcohol.^{32,35} However, the evidence that benzodiazepines increase the risk of delirium was considered less conclusive in subsequent studies.^{4,36,37} Hui highlighted the risks and benefits of benzodiazepines and concluded that the benefits from benzodiazepines for patients with agitated delirium depend on the clinicians' right selection.⁴ Remimazolam, as a novel benzodiazepine, is regarded as a promising agent in the field of anesthesia and sedation.³⁸ Its rapid onset of sedation has been observed starting at doses of 0.05 or 0.075 mg/kg, and the sedation depth and recovery time are dose-dependent.^{18,19} Compared with midazolam, remimazolam provides more effective sedation with faster recovery, lower incidence of hypotension and shorter time to restoration of neuropsychiatric function.^{12,39} Despite the lack of clinical trials on sedation in older or critically ill patients, the efficacy and excellent safety profile of remimazolam for endoscopic sedation and for anesthesia in vulnerable patients have been demonstrated.^{40–42} The above findings provide a basis and reference for our study.

In this study, loading doses of both study drugs were prescribed and administered in order to effectively induce calmness. Compared with dexmedetomidine, patients sedated with remimazolam besylate achieved target sedation earlier, but experienced more oversedation after a loading dose administration. These findings suggest that an individualized approach should be taken to select the loading dose of remimazolam besylate. In the older population, it may be safer to initiate titration from a lower dose (eg, 0.05 mg/kg). Due to the lack of referable research data, RASS-directed dose titration was used for subsequent maintenance sedation. The final results showed that the actual mean maintenance doses of remimazolam besylate and dexmedetomidine were 0.12 and 0.51 $\mu\text{g/kg/h}$, respectively. Of the patients sedated with remimazolam besylate, six actually had a mean maintenance dose below the predefined range, while only one received sedation rescue. In addition, no hypoxemia occurred and the incidence of hypotension was also significantly lower than that in the dexmedetomidine group during the continuous infusion. We suggest that maintenance doses of remimazolam besylate for sedation in non-intubated older patients should also be titrated from lower dose (eg, 0.1 mg/kg/h).

The MASS score is developed from the Sedation-Agitation Scale and includes seven individual tiers ranging from 0 (unresponsive) to 6 (dangerously agitated).⁴³ In this study, different MAAS scores were used to determine acute agitation and to assess resolution of agitation. A MAAS score of 5 to 6 indicates that the patient experienced uncooperative agitated behaviors, while a score of 2 to 4 indicates that the patient is calm and cooperative.¹⁷ There was no difference in the time to resolution of agitation between the two groups, implying similar efficacy of the two study drugs in relieving acute agitation. Since our study employed an intermittent awakening protocol, the time within the sedation target range was lower than that reported in previous study.²⁴ As a secondary outcome, this indicator was statistically different between the two groups, patients treated with remimazolam besylate attained the sedation target more frequently. We believe that the high controllability and predictability of remimazolam besylate facilitates “switching” between sedation and arousal, avoiding frequent and uncontrollable fluctuations in consciousness.⁴⁴ The “soft pharmacology”⁴⁵ of remimazolam enhanced our confidence in applying this novel benzodiazepine to control acute agitation symptoms. However, whether it is detrimental to the recovery from delirium is a matter of concern to us at the outset. In general, participants in this study experienced a shorter duration of sedation or delirium compared to previous studies.^{6,24,46} We speculated that this could be related to the inclusion of patients who underwent elective orthopedic surgery in this study. The study subjects had better health conditions compared to those critically ill patients who required organ function support, and the predisposing factors for delirium such as pain, immobilization, anemia, electrolyte disorders were also gradually removed after effective surgical treatment and other medical interventions. Therefore, refractory or frequently recurrent agitation or delirium was not observed in this study. Nonetheless, a longer time to delirium resolution was found in the remimazolam besylate group. Although the relationship between sedatives and delirium is complex and uncertain, the modulation of gamma-aminobutyric acid type A receptors by both benzodiazepines and opioids is related with delirium.^{33,47} As a result, delayed resolution of delirium associated with remimazolam still requires attention.

There are several limitations that need to be discussed. First, this is a single-blind clinical trial performed at a single center, more multicenter studies with larger samples are urgently required. Second, given the risk of agitation-related adverse events, a placebo control group was not established, but a regular dose of dexmedetomidine was selected as a comparator medication. Third, the study designed an intermittent awakening protocol, which avoided the bias in delirium assessment due to sedation.

However, the assessment every 8 hours and the small sample size may not be adequate to detect the difference in time to agitation resolution between the two groups. Finally, the particularity of the study subjects restricts the generalizability of our results. For safety reasons, the administration of the test drugs was done in the ICU, but the subjects did not fall into the category of critically ill patients because they hardly need organ function support. Therefore, the effects of remimazolam on agitated delirium in critically ill patients need to be further explored.

Conclusions

Among non-intubated older patients with agitated delirium after orthopedic surgery, the appropriate dose of remimazolam besylate was equally effective in relieving symptoms of agitation compared with dexmedetomidine, and resulted in earlier achievement of sedation goal as well as more controllable sedation. Meanwhile, the incidence of hypotension was lower, but the risks of dose-dependent oversedation and delaying delirium resolution should be noted. The findings provide an alternative to symptomatic treatment of agitated delirium, especially for patients with uncooperative or even dangerous agitation, remimazolam may be an appropriate agent for obtaining rapid tranquillisation.

Data Sharing Statement

The datasets for this study is available from the corresponding author (Email: qin18716111836@126.com) on reasonable request.

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Disclosure

The authors declare no conflicts of interest in this work.

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