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ORIGINAL ARTICLE

Retrospective comparison of the effects of remimazolam and dexmedetomidine on postoperative delirium in elderly patients undergoing orthopedic surgery of the lower extremities under spinal anesthesia

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Abstract

Purpose Remimazolam is often used for perioperative sedation due to its rapid onset and offset. However, the possible association between remimazolam and postoperative delirium (POD) remains undetermined. The present study evaluated whether remimazolam increased the incidence of POD compared with dexmedetomidine in elderly patients undergoing orthopedic surgery of the lower extremities.

Methods This retrospective study included patients aged ≥ 65 years who had undergone orthopedic surgery of the lower extremities under spinal anesthesia from January 2020 to November 2022 and were sedated with continuous intravenous infusion of dexmedetomidine or remimazolam. The incidence of POD was assessed through a validated comprehensive review process of each patient's medical records. The effect of remimazolam on the occurrence of POD compared with dexmedetomidine was evaluated by propensity score weighted multivariable logistic models.

Results A total of 447 patients were included in the final analysis. The crude incidence of POD within 3 days after surgery was 7.5% (17/226) in the dexmedetomidine group and 11.8% (26/221) in the remimazolam group, increasing to 9.7% (22/226) and 15.8% (35/221), respectively (p = 0.073), within 5 days. The multivariable models showed that, compared with dexmedetomidine, intraoperative sedation with remimazolam significantly increased the occurrence of POD within 3 days (odds ratio [OR] 2.21, 95% confidence interval [CI] 1.31 to 3.82, p = 0.003) and 5 days (OR 2.10, 95% CI 1.32 to 3.40, p = 0.002).

Conclusion Compared with dexmedetomidine, remimazolam infusion may be associated with a higher risk of POD in elderly patients undergoing orthopedic surgery of the lower extremities under spinal anesthesia.

Keywords Remimazolam · Dexmedetomidine · Postoperative delirium · Spinal anesthesia · Benzodiazepines

Introduction

The aging of the population has presented a challenge in patients undergoing surgery [1]. Advanced age has been found to be an independent risk factor for unfavorable postoperative outcomes, including postoperative delirium (POD) [2, 3]. The incidence of POD in elderly patients ranges from 3 to 50% [4], with POD having a detrimental effect on patients' overall clinical trajectory [5, 6].

Although the causes of POD and the exact mechanisms underlying its development in elderly patients remain unclear, several risk factors have been identified, including pre-existing cognitive impairment, type of surgery, coexisting chronic illnesses, and the use of specific medications

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[7–10]. Despite most of these risk factors being difficult or even impossible to correct, recent guidelines have provided several recommendations for reducing POD, such as comprehensive cognitive screening, avoiding perioperative polypharmacy and prolonged fasting, non-pharmacological interventions, and multimodal pain control [10, 11]. The effects of perioperative use of benzodiazepines remain unclear [12], with several guidelines recommending that benzodiazepines be avoided in high-risk patients [8, 13–15].

The incidence of POD has been reported to be lower in patients receiving dexmedetomidine than other agents, leading to guidelines recommending that dexmedetomidine be used for intraoperative sedation [16–18]. However, although considered relatively safe in elderly patients, dexmedetomidine has significant disadvantages, such as slow onset and unfavorable hemodynamic consequences, such as bradycardia and hypotension [19, 20].

Remimazolam is a benzodiazepine with an ultra-short duration of action that has been approved recently for use in perioperative sedation [21]. Unlike traditional benzodiazepines, remimazolam is rapidly metabolized by tissue esterases, which generate inactive metabolites, with its metabolism being independent of liver or kidney function [22]. This unique pharmacokinetic profile allows for the rapid achievement of the desired level of sedation without compromising swift recovery after the procedure. Because remimazolam has an ultra-short duration of action and generates inactive metabolites, remimazolam may not induce POD in elderly patients [23, 24], making it a suitable alternative to dexmedetomidine for intraoperative sedation. To date, however, the effects of remimazolam on the incidence of POD remains elusive.

To better understand the effects of intraoperative remimazolam on POD, we retrospectively compared the incidence of POD in elderly patients who received intraoperatively infusion of dexmedetomidine or remimazolam for sedation during orthopedic surgery of the lower extremities under spinal anesthesia.

Materials and methods

Study design and subjects

This single center, retrospective observational study was conducted at Chungnam National University Hospital, Republic of Korea. The study was approved by the Chungnam National University Hospital Institutional Review Board (Daejeon, Korea, IRB number: 2023–04-024, investigator: Soomin Lee, approval date: May 14, 2023), which waived the requirement for written informed consent due to the retrospective nature of the study. The study was registered in the Clinical Trial Registry of Korea (KCT0008571, principal investigator: Soomin Lee). Patients were included if they were aged ≥ 65 years; had undergone elective orthopedic surgery on their lower extremities under spinal anesthesia between January 1, 2020, and November 30, 2022; and were intraoperatively sedated by intravenous infusion of dexmedetomidine or remimazolam. Patients with preoperative cognitive dysfunction, incomplete medical records, or postoperative hospital stay < 5 days were excluded from the study.

Anesthesia and intraoperative sedation

During the study period, the institutional protocol for spinal anesthesia in patients undergoing lower limb surgery included 0.5% hyperbaric bupivacaine 8–14 mg, with or without intrathecal 20 μg fentanyl or 100 μg morphine at the discretion of the attending anesthesiologist.

The patients were designated as dexmedetomidine group or remimazolam group based on the primary sedative used. The institutional protocol for intraoperative sedation consisted of either (1) dexmedetomidine: 1 μg/kg infused over 10 min, followed by a continuous infusion of 0.4–1 μg/kg/hr; or (2) remimazolam: 3 mg/kg/hr infused over 2 min (0.1 mg/kg of loading dose) or 1 mg/kg/hr infused over 10 min (0.17 mg of loading dose) followed by a continuous infusion of 0.5 mg/kg/hr. All dosages were based on ideal body weight and were adjusted by the attending anesthesiologist to achieve moderate to deep sedation (Richmond Agitation & Sedation Scale −3 to −4).

Outcomes

The main study outcomes were the incidences of POD within 3 and 5 days after surgery. The occurrences of delirium and pre-existing cognitive dysfunction were evaluated through a comprehensive review of each patient's medical records with a validated method, Chart-based Delirium Identification Instrument (CHART-DEL) [25]. This review process encompassed routine baseline assessment upon admission, previous diagnoses, progress notes, consultations, and nursing notes recorded during regular nursing rounds (every 4– 8 h). The baseline assessment included evaluating patients' orientation (time, place, person) along with their ability for verbal communication. Reviews were performed by a trained researcher (JJ) who was unaware of the sedative agent used; if POD was unclear, a consensus was reached through discussions with another trained researcher (SL).

Patient characteristics and covariates

Patient characteristics included in the analysis were age, sex, body mass index (BMI), American Society of Anesthesiologist physical status, Charlson comorbidity index (CCI) [26], comorbidities (hypertension, diabetes mellitus, chronic kidney disease, cerebrovascular disease), intraoperative data (fluid intake, vasoactive agent use, transfusion, supplementary use of midazolam), and type of surgery (knee arthroplasty, hip arthroplasty, femur, and others). Vasoactive agent use was calculated as (total phenylephrine dose/50 μg) + (total ephedrine dose/5 mg).

Statistical analysis

Estimating the incidence of POD, especially in the remimazolam group, proved challenging due to the drug's novelty. Therefore, we pragmatically determined our study's sample size using data from a previous study that compared the impact of remimazolam and propofol on POD within 3 postoperative days in patients undergoing orthopedic surgery [27]. In this previous study, the incidence of POD in subjects who received intraoperative remimazolam was 15.6% among 147 individuals. We aimed to include an equivalent or larger number of subjects in the present study.

All statistical analyses were performed using R software version 4.2.2 (R Project for Statistical Computing, Vienna, Austria). Multiple imputations using chain equations (MICE package in r) were performed for missing values [28]. Continuous variables are presented as medians and interquartile ranges (IQRs) and compared by Mann–Whitney *U* tests, whereas categorical variables are presented as numbers (%) and compared by the chi-square test.

Potential selection bias in sedative use was addressed by employing multivariable models with propensity score weighting using the 'twang' package in R [29]. This package uses gradient boosted models and allows for flexible approaches that automatically account for nonlinearities and interactions among the covariates. In calculating propensity scores, the sedative agent (i.e., group) was defined as the dependent variable, with patient factors and clinical characteristics regarded as covariates to estimate the average treatment effect. A standardized mean difference (SMD) > 0.1 was considered the threshold for group imbalance. All the covariates were included in the final logistic models with propensity score weighting to estimate the group effect on the incidence of POD (i.e., doubly robust estimation) [30]. Issues of low event per variable and separation problems in logistic regression were addressed by applying Firth's bias reduction method using the 'logistf' package in R [31, 32].

Subgroup analysis I: exclusion of patients with supplementary midazolam use

To address the potential confounding effect of midazolam on POD, a subgroup analysis was conducted by excluding patients who received supplementary midazolam from the entire dataset. Multivariable models, employing the same covariates as in the main analysis, were then generated to evaluate any changes resulting from the exclusion in the outcome.

Subgroup analysis II: dexmedetomidine group

Due to the unique drug characteristics of dexmedetomidine, such as its arousable nature and slow onset, some patients in this group required small doses of midazolam. The impact of the supplementary use of midazolam on POD was assessed by employing additional multivariable logistic models in the dexmedetomidine group.

Sensitivity analysis

The missing values for BMI were found to be not missing at random (MAR), but rather more likely to be influenced by the occurrence of femur or hip fractures. To assess any potential bias resulting from the imputation process, four additional datasets were generated. In these datasets, values ranging from 5 to 20 were subtracted from the imputed BMIs under the MAR assumption [33]. The changes in coefficients were then examined by comparing the results obtained from these different datasets.

Results

A total 544 patients were assessed for eligibility. Among them, 97 patients were excluded, including three with insufficient records; 62 with pre-existing cognitive impairment; and 35 who stayed in hospital for < 5 days. Ultimately, 447 patients, 226 administered dexmedetomidine and 221 administered remimazolam, were analyzed (Fig. 1). The 33 missing BMI values and 2 missing values for intraoperative fluid intake were imputed as described. The clinical characteristics of the included patients are summarized in Table 1. After applying propensity score weighting, the SMDs for BMI (0.108) and type of surgery (0.199) remained above the threshold of 0.1, indicating residual group imbalance. Supplemental midazolam was administered only to patients in the dexmedetomidine group and was therefore not included in the propensity score calculation and subsequent multivariable analysis.

The crude rates of POD in the dexmedetomidine and remimazolam groups were 7.5% (17/226) and 11.8% (26/221),

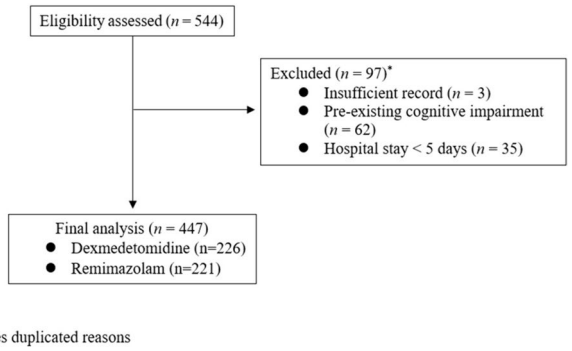

Fig. 1 Patient flow diagram

respectively, within 3 days of surgery (p = 0.174) and 9.7% (22/226) and 15.8% (35/221), respectively, within 5 days of surgery (p = 0.073) (Table 2). The multivariable models showed that, compared with dexmedetomidine, remimazolam infusion significantly increased the occurrence of POD within 3 days (odds ratio [OR] 2.21, 95% confidence interval [CI] 1.31 to 3.82, p = 0.003) and 5 days (OR 2.10, 95% CI 1.32 to 3.40, p = 0.002). In addition, advanced age, hip arthroplasty, and femur surgeries were significantly associated with the occurrence of POD within 3 and 5 days, whereas male gender was only associated with POD within 5 days. The propensity weighted multivariable logistic models are summarized in Table 3, and the process of propensity weighting is summarized in Supplementary material 1.

Table 1 Demographic and clinical characteristics of patients administered dexmedetomidine or remimazolam

	Dexmedetomidine (n = 226)	Remimazolam (n = 221)	Unweighted SMD	Weighted SMD
Age (yr)	75.0 (70.0, 80.0)	74.0 (70.0, 80.0)	0.067	0.005
Sex (male)	57 (25.2)	59 (26.7)	0.034	0.065
BMI (kg/m^2)	24.3 (22.2, 26.8)	25.6 (23.2, 27.9)	0.355	0.108
ASA > 2	84 (37.2)	82 (37.1)	0.001	0.046
CCI	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	0.006	0.022
HTN	152 (67.3)	155 (70.1)	0.062	0.015
DM	56 (24.8)	60 (27.1)	0.054	0.021
CKD	15 (6.6)	22 (10.0)	0.120	0.082
CVD	27 (11.9)	25 (11.3)	0.020	0.024
Fluid intake (L)	1.0 (0.6, 1.2)	0.8 (0.6, 1.1)	0.210	0.071
Transfusion*	13 (5.8)	8 (3.6)	0.101	0.030
Vasoactive use (n)**	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	0.029	0.040
Midazolam (n)***	63 (27.9)	0 (0.0)	0.879	0.842
Surgery type			0.438	0.199
Knee arthroplasty	83 (36.7)	118 (53.4)		
Hip arthroplasty	80 (35.4)	39 (17.6)		
Femur	38 (16.8)	36 (16.3)		
Others	25 (11.1)	28 (12.7)		

Standardized mean differences (SMD) are shown before and after propensity score weighting. Values are reported as number (%) or median (IQR).

SMD standardized mean difference, *BMI* body mass index, *ASA* American Society of Anesthesiologists physical status, *CCI* Charlson comorbidity index, *HTN* hypertension, *DM* diabetes mellitus, *CKD* chronic kidney disease, *CVD* cerebrovascular disease.

*Any use of packed red blood cells or fresh frozen plasma.

**Number of vasoactive agents used (total dose divided by 50 μg phenylephrine or 5 mg ephedrine).

***Not included in the propensity score calculation or the multivariable logistic model

Table 2 Postoperative delirium (POD) in dexmedetomidine and remimazolam groups

	Dexmedetomidine (n = 226)	Remimazolam (n = 221)	*p*
POD within 3 days (crude incidence)	17 (7.5)	26 (11.8)	0.174
POD within 5 days (crude incidence)	22 (9.7)	35 (15.8)	0.073
POD onset (days)	1.5 (1.0, 3.0)	1.0 (1.0, 4.0)	0.868

Values are number (%) or median (IQR)

Table 3 Result of propensity weighted multivariable logistic models for postoperative delirium (POD)

	POD within 3 days			POD within 5 days		
	OR	95% CI	*p*	OR	95% CI	*p*
Sedative (remimazolam)	2.21	1.31 to 3.82	0.003	2.10	1.32 to 3.40	0.002
Age (yr)	1.08	1.03 to 1.13	0.001	1.06	1.02 to 1.11	0.002
Sex (male)	1.61	0.90 to 2.84	0.109	2.15	1.30 to 3.56	0.003
BMI (kg/m^2)	1.02	0.94 to 1.11	0.612	1.05	0.98 to 1.13	0.178
ASA > 2	1.42	0.70 to 2.82	0.321	1.14	0.60 to 2.11	0.680
CCI	1.07	0.89 to 1.26	0.461	1.04	0.88 to 1.21	0.654
HTN	1.41	0.77 to 2.65	0.269	1.58	0.92 to 2.79	0.102
DM	1.02	0.52 to 1.93	0.954	0.94	0.52 to 1.67	0.841
CKD	1.60	0.64 to 3.82	0.305	2.04	0.91 to 4.49	0.083
CVD	0.71	0.30 to 1.61	0.418	1.15	0.55 to 2.37	0.700
Fluid intake (L)	0.92	0.39 to 2.27	0.937	0.74	0.33 to 1.59	0.444
Transfusion*	0.37	0.07 to 1.49	0.174	0.33	0.06 to 1.28	0.114
Vasoactive use (n)**	0.92	0.78 to 1.07	0.292	0.91	0.79 to 1.05	0.194
Surgery site***						
Knee arthroplasty	NA	NA	NA	NA	NA	NA
Hip arthroplasty	8.12	3.63 to 19.67	< 0.001	5.58	2.88 to 11.12	< 0.001
Femur	7.42	2.81 to 20.95	< 0.001	5.10	2.24 to 11.95	< 0.001
Others	2.27	0.63 to 7.67	0.204	1.35	0.45 to 3.76	0.577

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *ASA* American Society of Anesthesiologists physical status, *CCI* Charlson comorbidity index, *HTN* hypertension, *DM* diabetes mellitus, *CKD* chronic kidney disease, *CVD* cerebrovascular disease, *NA* not available.

*Any use of packed red blood cells or fresh frozen plasma.

**Number of vasoactive agents used (total dose divided by 50 μg phenylephrine or 5 mg ephedrine).

***Knee arthroplasty was regarded as a reference

The result of the first subgroup analysis after excluding patients who received supplementary midazolam (n = 63) is summarized in Table 4. The ORs for POD within 3 and 5 days increased to 3.77 (95% CI 1.95 to 7.73, p < 0.001) and 3.23 (95% CI 1.84 to 5.91, p < 0.001). The second subgroup analysis in dexmedetomidine group showed that the use of supplementary midazolam was significantly associated with POD within 3 days (OR 4.69, 95% CI 1.48 to 16.21, p = 0.009) and 5 days (OR 3.86, 95% CI 1.40 to 11.13, p = 0.009) (Supplementary material 2).

Sensitivity analyses showed that the results remained largely unchanged in the other imputed datasets, suggesting that the results of this study are robust and not heavily influenced by the specific imputation method used (Supplementary material 3).

Discussion

Previous studies suggest that the action duration of benzodiazepines in the perioperative period may affect the incidence of POD [23, 24]. Due to its brief action duration, remimazolam may be beneficial when performing sedation in elderly patients for reducing POD. Therefore, we retrospectively compared the incidence of POD in elderly patients who received either remimazolam or dexmedetomidine while undergoing orthopedic lower-limb surgery under spinal anesthesia. Our results do not favor remimazolam over dexmedetomidine for intraoperative sedation, as remimazolam was associated with a higher risk of POD.

POD is the most common complication in elderly surgical patients. The present study found that the incidence of POD in the remimazolam group 3 days after surgery was 11.8%, in good agreement with the results of a previous prospective trial, which reported that the incidence of POD after intraoperative remimazolam use in patients undergoing orthopedic surgery was 15.6% [27]. However, our results differ from previous large-scale retrospective studies which reported incidences of about 2–3% [23, 34]. These studies relied on the International Classification of Disease codes to assess POD, whereas the present study employed a validated assessment tool to evaluate POD [25]. To enhance the reliability of the results, medical records of individual patients were comprehensively reviewed by trained

Table 4 Result of propensity weighted multivariable logistic models for postoperative delirium (POD) after excluding patients who received supplementary midazolam (subgroup analysis I)

	POD within 3 days			POD within 5 days		
	OR	95% CI	*p*	OR	95% CI	*p*
Sedative (remimazolam)	3.77	1.95 to 7.73	< 0.001	3.23	1.84 to 5.91	< 0.001
Age (yr)	1.06	1.00 to 1.11	0.035	1.04	0.99 to 1.09	0.094
Sex (male)	2.51	1.27 to 4.95	0.009	2.48	1.37 to 4.47	0.003
BMI (kg/m^2)	1.06	0.96 to 1.17	0.231	1.07	0.98 to 1.16	0.115
ASA > 2	1.36	0.59 to 3.06	0.464	1.00	0.48 to 2.02	0.995
CCI	1.12	0.92 to 1.36	0.240	1.12	0.94 to 1.33	0.201
HTN	1.32	0.64 to 2.84	0.455	1.67	0.88 to 3.32	0.119
DM	1.54	0.71 to 3.24	0.269	1.11	0.56 to 2.12	0.761
CKD	1.11	0.37 to 3.14	0.843	1.68	0.66 to 4.16	0.271
CVD	0.96	0.36 to 2.43	0.933	1.05	0.44 to 2.42	0.915
Fluid intake (L)	1.37	0.48 to 3.67	0.55	0.93	0.37 to 2.21	0.870
Transfusion*	0.26	0.03 to 1.47	0.135	0.28	0.04 to 1.43	0.135
Vasoactive use (n)**	0.85	0.68 to 1.03	0.099	0.88	0.73 to 1.03	0.121
Surgery site***						
Knee arthroplasty	NA	NA	NA	NA	NA	NA
Hip arthroplasty	12.23	4.85 to 34.44	< 0.001	6.26	2.98 to 13.59	< 0.001
Femur	11.65	3.73 to 40.45	< 0.001	6.28	2.47 to 16.69	< 0.001
Others	2.26	0.44 to 9.80	0.307	1.21	0.32 to 3.94	0.768

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *ASA* American Society of Anesthesiologists physical status, *CCI* Charlson comorbidity index, *HTN* hypertension, *DM* diabetes mellitus, *CKD* chronic kidney disease, *CVD* cerebrovascular disease, *NA* not available.

*Any use of packed red blood cells or fresh frozen plasma.

**Number of vasoactive agents used (total dose divided by 50 μg phenylephrine or 5 mg ephedrine).

***Knee arthroplasty was regarded as a reference

personnel. Additionally, the present study included various clinical confounding factors in propensity score weighting and subsequent multivariable logistic regression analyses. These techniques were incorporated to minimize selection bias as well as any residual imbalances that remained after propensity score weighting.

Limited data are currently available regarding POD following the intraoperative use of remimazolam. Recent prospective trials have reported that the incidence of POD did not differ significantly between patients receiving intraoperative remimazolam and other anesthetics, such as propofol and inhalation agents [27, 35]. However, direct comparisons with these studies are challenging due to differences in the control group (propofol or inhalation agents vs. dexmedetomidine) and variations in types of anesthesia (general vs. spinal anesthesia). Most importantly, many of these studies included the concurrent use of other anesthetics, limiting the ability to fully assess the impact of remimazolam on the observed outcomes. Although a recent retrospective study found that the incidence of POD was lower in patients receiving remimazolam than propofol for general anesthesia during transcatheter aortic valve implantation [36], that study was limited by its small sample size (n = 98) and insufficient consideration of confounding factors. The routine use of flumazenil in the remimazolam group, which differs from other studies, may have also affected the result.

In clinical practice, the use of supplementary sedatives during dexmedetomidine sedation is relatively common due to its slow onset and arousability. Of the 226 patients in the present study administered dexmedetomidine, 63 (27.9%) were treated with supplementary midazolam. A recent randomized trial also reported a high rate of rescue midazolam administration (39.2%) during dexmedetomidine sedation in patients undergoing orthopedic surgery [20]. Thus, the results of the current study provide a more realistic reflection of clinical practice, as they account for the supplementary sedation often needed during dexmedetomidine administration. Interestingly, the second subgroup analysis showed that the risk of POD was higher when supplementary midazolam was administered to patients in the dexmedetomidine group. These findings are in agreement with the known unfavorable effects of

conventional benzodiazepines on POD, suggesting that the estimated risk of POD in the remimazolam group relative to the dexmedetomidine group may be underestimated. This was further supported by the first subgroup analysis, which showed an increased odds ratio for POD in the remimazolam group after excluding patients who received supplementary midazolam. While our subgroup analysis may provide more refined and specific insights regarding the effects of remimazolam regarding POD, we considered the results from the whole dataset (including patients with supplementary midazolam) to be more clinically relevant.

POD has been associated with various risk factors, including age, gender, preexisting cognitive impairment, type and duration of surgery, postoperative pain, hypothermia, and blood transfusion [37]. Despite this study only enrolling patients aged ≥ 65 years, the risk of POD still increased with age, in agreement with results showing that age is a key predictor of POD in various clinical settings. Similarly, the finding that male gender was a risk factor for POD in the present study is in agreement with previous results [38, 39]. Although a recent meta-analysis reported conflicting results [40], this inconsistency could be attributed to the broad age range (from 18 years) of patients in the studies included in the meta-analysis. The other risk factor for POD identified in the present study, hip and femur surgery, may reflect patient vulnerabilities, such as frailty and functional dependency, which are also risk factors for POD [41, 42].

This study has several limitations. First, its retrospective design prevented a quantitative assessment of baseline cognitive function. Although subjects with apparent cognitive dysfunction could be excluded through our comprehensive review process, subtle or equivocal states could have been missed. Second, the tool used for assessing POD (CHART-DEL) may not fully capture hypo- or mixed-type delirium, potentially leading to the underdiagnosis of delirium. Third, the study included patients treated at a single center, which may limit the generalizability of the findings. Additional studies in different settings are necessary to establish the broader applicability of these results. Fourth, despite a single institutional protocol for sedation, the lack of detailed records of sedation depth raises the possibility of discrepancies in sedation depth between subjects. Given the potential association between sedation depth and POD [43], it is conceivable that the reported effect size represents a combined effect of the direct impact of the sedative type and any mediating effect of sedation depth. Fifth, the effects of postoperative pain, another well-established POD risk factor [11], was not included in the present study. However, it is important to note that postoperative pain occurs after the exposure, thus constituting a 'post-exposure' variable. Given that explicit determination of causal relationships among the exposure, post-exposure, and outcome variables is challenging, it is often advisable to refrain from adjusting for covariates that occur temporally subsequent to the exposure [44]. Thus, postoperative pain or measures of postoperative analgesia were not included in the current study.

In conclusion, despite its brief action duration, intraoperative sedation using remimazolam infusion may be associated with a higher risk of POD compared to dexmedetomidine in elderly patients undergoing orthopedic lower limb surgery under spinal anesthesia. While our results agree with previous studies favoring the beneficial impact of dexmedetomidine over benzodiazepines regarding POD, further well-designed prospective studies are needed to confirm the potential harm of remimazolam.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00540-024-03386-6.

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Declarations

Conflict of interest No potential conflict of interest relevant to this article was reported.

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