Clinical effectiveness of intraoperative continuous pump infusion of remimazolam on postoperative delirium in elderly patients with hip fractures

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Abstract. Postoperative delirium (POD) is a prevalent acute central nervous system complication in elderly patients following surgery. The potential of remimazolam, a novel ultrashort-acting benzodiazepine, in mitigating POD after hip fracture surgery remains unclear. The present study aimed to investigate the effects of continuous intraoperative remimazolam infusion on POD in elderly patients with hip fractures undergoing subarachnoid block. A retrospective analysis was conducted on 405 elderly patients who underwent elective hip fracture surgery under subarachnoid block at The 904th Hospital of the Joint Logistics Support Force (Wuxi, China) between January 2019 and December 2023. Patients were divided into two groups based on the intervention received: The remimazolam group (observation group, n=180) and the control group (no remimazolam treatment, n=225). POD was evaluated using the Confusion Assessment Method-Chinese Revision at 1-7 days post-surgery. Anxiety scores were recorded 1 day before and 1 day after surgery. The incidence of intraoperative hypertension, hypotension, bradycardia, hypoxemia, and postoperative nausea and vomiting was also documented. Baseline characteristics were comparable between the two groups, with no significant differences observed in patient demographics. The incidence of POD was significantly lower in the remimazolam group compared with that in the control group (P=0.008). Anxiety scores 1 day post-surgery were also significantly reduced in the remimazolam group (P<0.001). Furthermore, the remimazolam group demonstrated a marked reduction in intraoperative hypertension (P=0.017). No significant differences were observed between the two groups regarding the incidences of intraoperative hypotension, bradycardia, hypoxemia, or postoperative nausea and vomiting. In conclusion, remimazolam appears to reduce the incidence of POD in elderly patients undergoing hip fracture surgery with subarachnoid block, potentially through the alleviation of intraoperative anxiety, without increasing the risk of perioperative complications.

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Introduction

Postoperative delirium (POD) is a prevalent acute central nervous system disorder in elderly patients following surgery, typically manifesting 24-72 h post-operation (1,2). POD contributes to a range of adverse outcomes, including increased postoperative complications, such as pneumonia, deep venous thrombosis and accidental injury, extended hospital stays, higher medical costs and elevated readmission rates (1,2). Inouye *et al* (3) reported that POD affects 11-51% of surgical patients, with the incidence notably higher in older adults undergoing joint replacement procedures. With an aging population, the number of elderly patients undergoing surgery has risen, with a study suggesting that up to 46% of these patients experience POD (3). Furthermore, previous research has indicated that delirium or POD may increase the long-term risk of developing dementia and mortality due to neuroinflammation and neuronal damage (4). In addition to its high morbidity, POD escalates treatment costs and hospital stay durations, placing a substantial financial burden on the healthcare system. In the United States, >2.6 million adults aged ≥65 years old experience delirium annually, resulting in an estimated $164 billion in healthcare expenses each year (4). Addressing the prevention and reduction of POD during the perioperative period is therefore of critical importance. However, the precise pathophysiological mechanisms of delirium remain unclear, complicating diagnosis and leading to frequent misdiagnosis or oversight. Currently, no specific medications are available for the treatment or prevention of delirium (2).

Remimazolam, a novel ultrashort-acting benzodiazepine, has gained notable attention for its potential in preventing and managing POD. It has been suggested that remimazolam may perioperatively reduce the incidence of POD (5).

A retrospective observational study found that elderly patients receiving remimazolam for maintenance anesthesia experienced markedly lower POD rates compared with those receiving alternative anesthetics, with remimazolam being independently associated with a reduced incidence of POD (6). Xue *et al* (7) similarly reported that perioperative administration of remimazolam notably decreased the occurrence of POD. A meta-analysis of 11 trials involving 1,985 participants indicated that remimazolam decreased the likelihood of POD after non-cardiac surgery than saline, although it was not superior to dexmedetomidine or propofol; however, remimazolam was associated with reduced intraoperative hypotension (5). On the other hand, another systematic review and meta-analysis indicated that the perioperative use of remimazolam did not markedly increase POD incidence but it was linked to a lower rate of intraoperative hypotension (8). Supporting this, in a prospective randomized controlled trial comparing remimazolam and propofol in orthopedic surgery for elderly patients, no significant difference was found in POD incidence between the two groups. However, the remimazolam group experienced longer postoperative extubation times and longer stays in the post-anesthesia care unit, although they had a lower incidence of postoperative hypotension (9). A prospective cohort study in cardiovascular surgery showed that remimazolam did not markedly increase POD incidence compared with other anesthetics, suggesting that it may be a safe option in cardiovascular procedures (10). Furthermore, Glumac *et al* (11) reported that preoperative corticosteroid administration can mitigate the inflammatory response induced by surgery, reducing the incidence and severity of cognitive impairment. Given that remimazolam also markedly alleviates the inflammatory response during the perioperative period, its potential to reduce POD is promising (12). However, its effects across various surgical types and patient populations require further investigation through large-scale trials. Notably, to the best of our knowledge, no large-scale study has yet examined the impact of remimazolam on delirium following hip fracture surgery. Additionally, previous studies did not involve continuous remimazolam infusion during hip fracture surgery (11,12).

Therefore, the present study aimed to evaluate the clinical efficacy of continuous remimazolam infusion during hip fracture surgery with subarachnoid block in elderly patients at risk for POD. A large sample of data from a single center were used, which to the best of our knowledge is rarely reported. Additionally, the study aimed to specifically investigate the role of remimazolam in the high-risk, vulnerable and understudied hip fracture population, where polypharmacy, frailty and specific surgical stressors might modulate drug effects differently.

Patients and methods

Study design and participant selection. A retrospective study involving 405 elderly patients who underwent elective hip fracture surgery under subarachnoid block was conducted at The 904th Hospital of the Joint Logistics Support Force (Wuxi, China) from January 2019 to December 2023. Participants were patients of both sexes, aged ≥65 years, with a BMI of 18.5-31.0 kg/m^2 and American Society of Anesthesiologists (ASA) (13) grades I-II. The median age was 68 years (range, 65-86) in the observation group and 69 years (range, 65-87) in the control group. The present study included 109 male and 71 female patients in the observation group, and 128 male and 97 female patients in the control group. Surgical procedures included hip replacement and femoral neck internal fixation. The study protocol was approved by the Ethics Committee of The 904th Hospital of the Joint Logistics Support Force, People's Liberation Army of China (approval no. 2024-002). All participants provided written informed consent. Exclusion criteria included: i) An inability to complete the Mini-Mental State Examination (14) or scoring below the minimum threshold for their educational level [<24 points (less than postsecondary education), <23 points (less than secondary education) or <20 points (less than primary education)]; ii) preoperative central nervous system disorders (such as dementia, Parkinson's disease or severe sequelae of cerebrovascular events); iii) prior use of antianxiety or antidepressant medications; iv) a history of drug or alcohol dependence; v) significant visual or hearing impairment; vi) pulmonary, hepatic or renal insufficiency; and vii) contraindications to spinal anesthesia (including the use of anticoagulants, coagulation disorders, spinal cord diseases or refusal of spinal anesthesia). Patients were also excluded due to the following reasons: Converted to general anesthesia during surgery, intraoperative blood loss of >400 ml, unplanned transfer to the intensive care unit (ICU) and lost to follow-up post-operation.

Specific anesthesia protocol. All patients were instructed to fast and abstain from drinking for ≥8 h prior to surgery. Upon arrival in the operating room, patients were administered oxygen via a mask at a flow rate of 4 l/min and peripheral venous access was established. Standard monitoring included an electrocardiogram and peripheral oxygen saturation (SpO_2) measurements. Radial artery puncture and catheterization were performed to monitor invasive blood pressure. Compound sodium acetate was infused at a rate of 5-7 ml/kg/h. Spinal anesthesia was performed with the patient in the knee-chest position with the affected side facing upward. After disinfection and draping, the L3-L4 or L2-L3 intervertebral space was selected for subarachnoid puncture. Once cerebrospinal fluid was aspirated, 2.0-2.5 ml heavy bupivacaine (1 ml 10% glucose + 2 ml 0.75% bupivacaine) was injected, with the upper limit of anesthesia targeted at T10-T12.

In the remimazolam group, an initial dose of 0.1 mg/kg remimazolam (diluted to 1 mg/ml and administered over 1 min) was followed by a continuous intravenous infusion at a rate of 0.2 mg/kg/h to maintain a modified observer's assessment of alertness/sedation (MOAA/S) score of 1 or 2. If the MOAA/S score was >2, a supplementary dose of remimazolam (0.05 mg/kg) was administered, with a minimum interval of 3 min between dose s until the MOAA/S score dropped to <2. The remimazolam infusion was discontinued after surgery. For intraoperative management, the following interventions were used if needed: 8 μg norepinephrine for hypotension [systolic blood pressure (SBP) <80% of baseline]; 0.2 mg nicardipine for hypertension (SBP >120% of baseline); 0.5 mg atropine for bradycardia (heart rate <45 beats/min); and jaw lifting or oxygen administration through a mask with pressure

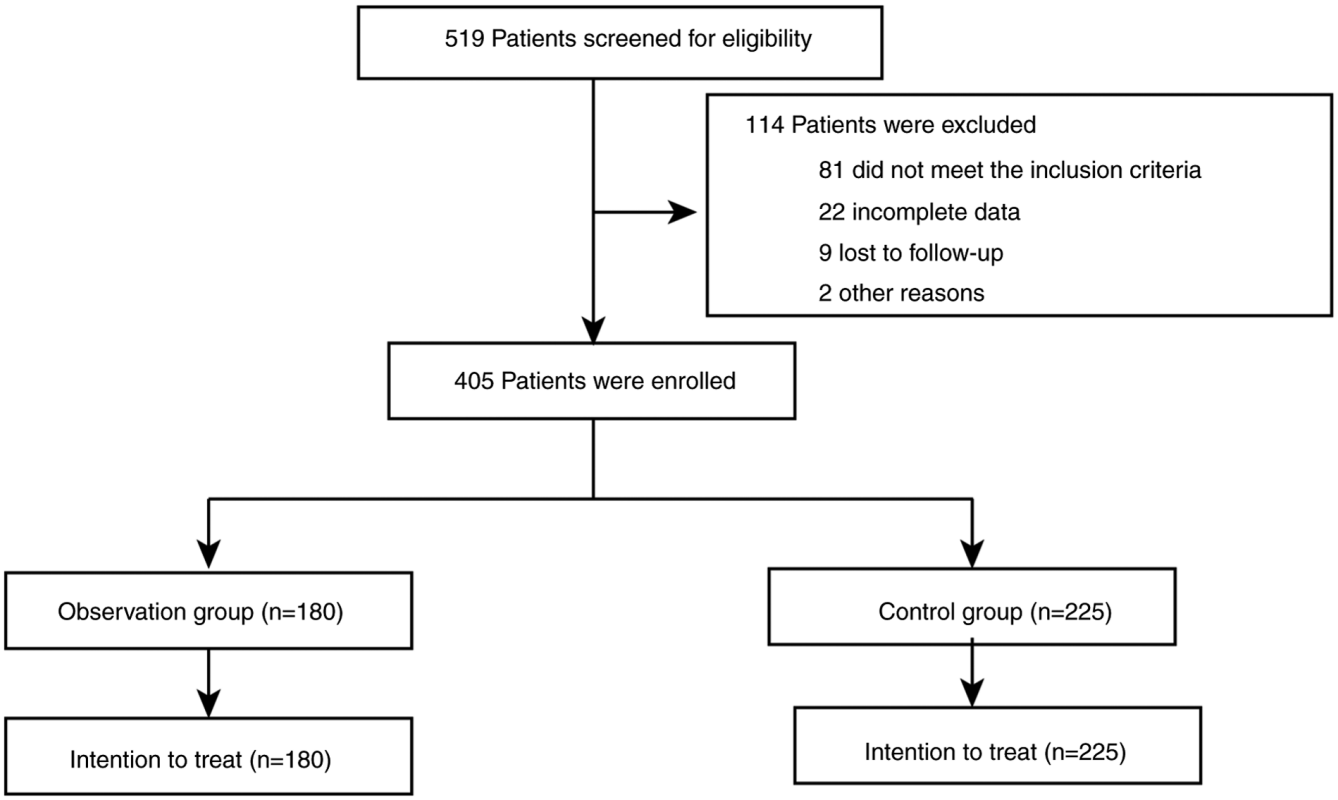

Figure 1. Patient recruitment and follow-up. Schematic diagram detailing how many patients were recruited and how many patients were excluded.

for hypoxemia (SpO_2 <90%), with oropharyngeal airway or laryngeal mask placement as necessary. The analgesic pump formula consisted of 1.5 μg/kg sufentanil, 0.25 mg palonosetron and 100 ml normal saline, with an infusion rate of 2 ml/h, a single press dose of 0.5 ml and a maximum infusion of 15 min. If the visual analogue scale (VAS) pain score was >3 points postoperatively and unrelieved by the analgesic pump, 50 mg flurbiprofen axetil was administered intravenously for rescue analgesia (15). In the control group, conventional sedation with propofol and analgesia was used without remimazolam. The initial propofol dosage was 1.0-1.5 mg/kg, followed by continuous intravenous infusion at a rate of 4-12 mg/kg/h to maintain a MOAA/S score of 1 or 2. Neither group received sedatives after surgery.

Observation indicators. Intraoperative blood loss, fluid infusion, operation time, anesthesia time and postoperative hospital stay were recorded. The Confusion Assessment Method-Chinese Revision (CAM-CR) was administered between 1 and 7 days after surgery by an experienced evaluator blinded to the intervention (16). POD occurrence was assessed twice daily, at 8:00-10:00 a.m. and 4:00-8:00 p.m. A POD diagnosis was made if the CAM-CR score was >22 at any point. The number of POD cases, the onset time (from the end of the operation to POD diagnosis) and the duration (from POD diagnosis to a CAM-CR score of ≤22 points) were documented. The number of patients who experienced POD was documented, with POD diagnosis indicating a positive case. The duration of POD was recorded during the entire 7-day period and the time when POD symptoms occurred was also documented. Anxiety scores were recorded 1 day before surgery and 1 day post-surgery. The State Anxiety Inventory (17) was used to assess anxiety 1 day before surgery, whereas the 7-item Generalized Anxiety Disorder scale (18) was used to evaluate anxiety 1 day post-surgery. VAS pain scores and the need for rescue analgesia on days 1-3 post-surgery were also collected. Additionally, incidences of intraoperative hypertension, hypotension, bradycardia, hypoxemia, and postoperative nausea and vomiting were monitored and recorded.

Statistical analysis. Statistical analyses were performed using SPSS software (version 20.0; IBM Corp) and GraphPad Prism 6.0 (Dotmatics). All data were verified by the data committee of the hospital. Data were first assessed for normality using the Shapiro-Wilk test. Continuous variables and data following a normal distribution are presented as the mean ± standard deviation. Quantitative data were analyzed using independent sample t-tests, while categorical data were compared using the χ^2 test or Fisher's exact test. Categorical scores are presented as median (IQR) and were analyzed using Mann-Whitney U test. A two-sided P-value <0.05 was considered to indicate a statistically significant difference. As the results of the univariate analysis did not fall <0.05, there was no need to conduct a multivariate analysis.

Results

Patient enrollment and baseline characteristics. After an initial assessment of 519 patients, 405 patients were enrolled in the study, with 180 in the observation group and 225 in the control group (Fig. 1). All patients were analyzed using

Table I. Comparison of baseline data.

Characteristic	Observation group (n=180)	Control group (n=225)	P-value
Age, years	68.29±7.15	69.06±7.46	0.294
Sex, n (%)			0.457
Male	109 (60.56)	128 (56.89)	
Female	71 (39.44)	97 (43.11)	
BMI, kg/m^2	23.12±1.98	22.94±1.91	0.354
ASA physical classification status, n (%)			0.184
I, Healthy	7 (3.89)	15 (6.67)	
II, Mild systemic disease	128 (71.11)	163 (72.44)	
III, Severe systemic disease	44 (24.44)	46 (20.44)	
IV, Severe, life-threatening disease	1 (0.56)	1 (0.44)	
Educational level, n (%)			0.805
<Elementary school	113 (62.78)	145 (64.44)	
Elementary school	45 (25.00)	51 (22.67)	
≥Secondary school	22 (12.22)	29 (12.89)	
Median MMSE[a] (IQR)	20 (17, 24)	20 (16, 25)	0.865
Preexisting dementia, n (%)	66 (36.67)	84 (37.33)	0.890
Preoperative delirium, n (%)	1 (0.56)	2 (0.89)	>0.999
Type of fracture, n (%)			-
Femoral neck	104 (57.78)	131 (58.22)	0.928
Intertrochanteric	68 (37.78)	87 (38.67)	0.855
Subtrochanteric	6 (3.33)	6 (2.67)	0.694
Femoral head	2 (1.11)	1 (0.44)	0.587
Risk factors			
Smoking history, n (%)	57 (31.67)	74 (32.89)	0.794
Hypertension, n (%)	119 (66.11)	154 (68.44)	0.619
Hyperlipidemia, n (%)	104 (57.78)	122 (54.22)	0.474
Diabetes, n (%)	51 (28.33)	66 (29.33)	0.825
Atrial fibrillation, n (%)	78 (43.33)	91 (40.44)	0.558
Living environment, n (%)			0.840
Town	75 (41.67)	96 (42.67)	
Countryside	105 (58.33)	129 (57.33)	
Intraoperative blood loss, ml	110.54±21.04	108.61±20.86	0.357
Intraoperative fluid infusion volume, ml	950.76±65.43	938.27±67.29	0.20
Operation time, min	62.18±15.63	65.44±14.09	0.395
Anesthesia time, min	98.07±18.95	97.72±19.87	0.857
Postoperative hospital stay, days	9.29±2.05	9.17±1.92	0.546

Data are presented as the mean ± SD unless otherwise indicated. [a]Maximum MMSE score is 30 points; <24 (less than postsecondary education), <23 (less than secondary education), or <20 (less than primary education). ASA, American Society of Anesthesiologists; MMSE, Mini-Mental State Examination.

the intention-to-treat approach. No statistically significant differences were found between the two groups regarding demographic characteristics, including sex, age, weight, BMI, ASA classification, educational level, comorbidities, intraoperative blood loss, intraoperative fluid infusion volume, operation time, anesthesia time or postoperative hospital stay (Table I).

Comparison of POD. The overall clinical efficacy of remimazolam measured by the incidence of POD was compared between the two groups. The total incidence of POD in the observation group was significantly lower than that in the control group (13.89% vs. 24.44%; P=0.008) (Table II; Fig. 2), and the duration of POD was also significantly shorter (49.17±10.28 h vs. 51.74±11.65 h; P=0.021). However, no statistically significant difference was observed in the onset time of POD between the groups (Table II).

Comparison of anxiety. After follow-up, anxiety scores were found to be similar between the two groups (Table III).

Table II. Comparison of the incidence of POD.

POD	Observation group (n=180)	Control group (n=225)	P-value
Incidence, n (%)	25 (13.89)	55 (24.44)	0.008
Onset time, h	25.19±8.11	26.11±8.47	0.269
Duration time, h	49.17±10.28	51.74±1.65	0.021

Data are presented as the mean ± SD unless otherwise indicated. POD, postoperative delirium.

Table III. Comparison of anxiety.

Anxiety	Observation group (n=180)	Control group (n=225)	P-value
1 day before operation[a]	35 (26, 45)	36 (25, 47)	0.670
1 day after operation[b]	6 (5, 9)	5 (7, 10)	0.015

Data are presented as the median (IQR). [a]The State Anxiety Inventory score; [b]the 7-item Generalized Anxiety Disorder scale.

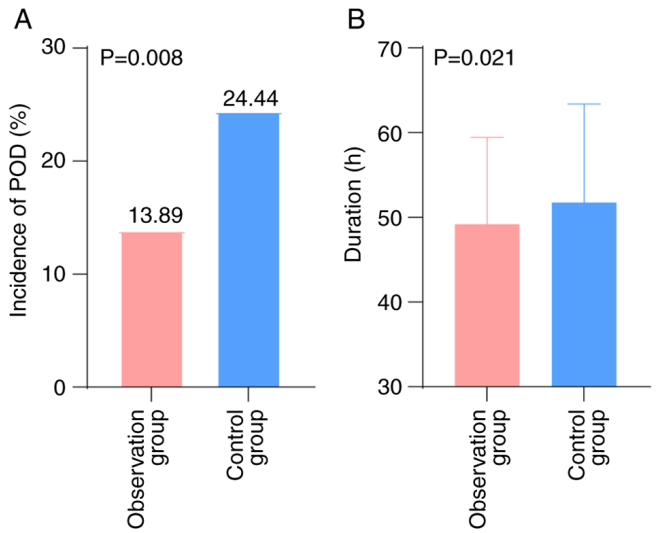

Figure 2. Incidence of POD in remimazolam vs. control groups. (A) Incidence of POD. (B) Duration of POD. POD, postoperative delirium.

However, the anxiety score 1 day post-surgery was significantly lower in the observation group (P=0.015) (Table III).

Comparison of VAS scores and pain. Regarding pain management, no significant differences were found in the VAS pain scores 1 or 3 days post-surgery, nor in the incidence of rescue analgesia between the groups (Table IV). By contrast, 2 days post-surgery the VAS pain score was significantly lower in the observation group than in the control group (P=0.046).

Comparison of complications. To evaluate the safety of remimazolam, the incidence of perioperative complications was compared. The observation group exhibited a significantly lower incidence of intraoperative hypertension (P<0.05). No significant differences were found in the incidences of intraoperative hypotension, bradycardia, hypoxemia, or postoperative nausea and vomiting between the two groups (Table V).

Discussion

In the present study, it was observed that the incidence of POD was significantly lower in elderly patients with hip fractures under subarachnoid block in the remimazolam group compared with that in the control group. However, there were no significant differences between the two groups regarding the onset time of POD. The anxiety scores on the 1st postoperative day and the incidence of intraoperative hypertension were also significantly reduced in the remimazolam group compared with those in the control group. No significant differences were noted in the incidence of intraoperative hypotension, bradycardia, hypoxemia, or postoperative nausea and vomiting between the two groups.

POD is a common complication in elderly patients with hip fractures undergoing subarachnoid block, particularly those undergoing hip replacement surgery (19-21). A previous study reported that the incidence of POD in elderly patients ranges from 4-53%, making POD one of the most prevalent surgical complications in this age group (22). Consistent with these findings, the present study revealed a high incidence of POD in elderly patients undergoing geriatric hip surgery. Elderly individuals face a notably increased risk of POD after hip surgery; however, the specific reason is unknown. Notably, POD can have profound implications for long-term prognosis, such as an increased incidence of dementia (2,23). The onset of POD is influenced by various factors, including advanced age, hip fracture surgery (as compared with elective hip surgery) (24,25), and preoperative cognitive impairment or delirium (19). POD not only impacts short-term recovery but can also contribute to long-term cognitive decline and other complications (26), such as urinary tract infections. Research has indicated that POD is associated with extended hospital

Table IV. Comparison of VAS scores and pain.

Variable	Observation group (n=180)	Control group (n=225)	P-value
VAS 1 day after operation	4 (2, 6)	4 (2, 6)	0.442
VAS 2 days after operation	2 (1, 3)	2 (1, 5)	0.046
VAS 3 days after operation	3 (2, 4)	3 (2, 4)	0.339
Remedial analgesia, n (%)	31 (17.22)	47 (20.89)	0.352

Data are presented as the median (IQR) unless otherwise indicated. VAS, visual analog scale.

Table V. Comparison of complications.

Complication	Observation group (n=180)	Control group (n=225)	P-value
Hypertension	11 (6.11)	30 (13.33)	0.017
Hypotension	19 (10.56)	34 (15.11)	0.177
Bradycardia	16 (8.89)	17 (7.56)	0.626
Hypoxemia	6 (3.33)	10 (4.44)	0.568
Nausea	13 (7.22)	19 (8.44)	0.650
Vomiting	9 (5.00)	12 (5.33)	0.881

Data are presented as n (%).

stays, increased medical complications and poorer short-term functional outcomes, such as psychological well-being (22). Therefore, effective management of POD should emphasize prevention and early detection. While the efficacy of medical preventive interventions is limited, a multidisciplinary approach, including adequate hydration, optimized analgesia, minimizing polypharmacy, active physical therapy and early identification of delirium symptoms, has been shown to effectively reduce the incidence of POD (22).

Progress has been made in the treatment and pharmacological management of POD in elderly patients undergoing hip surgery (27,28). Multidisciplinary comprehensive care is widely regarded as one of the most effective strategies for preventing and treating POD. By predicting perioperative risks, avoiding certain medications and providing integrated geriatric care, the incidence of POD can be substantially reduced (29). Early identification and intervention are critical for improving patient outcomes; therefore employing validated, user-friendly bedside diagnostic tools, such as the CAM-CR scale, to screen for POD allows healthcare professionals to promptly detect and manage delirium (30). Research into pharmacological prophylaxis is also advancing; among pharmacological interventions, dexmedetomidine and multimodal analgesia have shown potential in managing POD; however, the adverse effects of antipsychotic drugs must be considered (29). While routine drug use for prevention is not yet recommended, the effectiveness of multicomponent preventive strategies has been well established and should be incorporated into clinical practice (30). Despite evidence from numerous clinical studies demonstrating that drugs such as dexmedetomidine reduce POD, some studies have found them ineffective or even associated with an increased incidence of complications, such as hypotension and bradycardia (31-33). A randomized clinical trial examining dexmedetomidine use in elderly patients undergoing major elective noncardiac surgery found no notable reduction in POD with its intraoperative use (31). This study suggested that while dexmedetomidine was linked to lower delirium rates in ICUs, its use during surgery did not yield the same benefits, indicating that the timing of administration may be a key factor in determining its efficacy. Similarly, a study on oral and maxillofacial surgery demonstrated that perioperative dexmedetomidine use did not notably impact the incidence of POD (29). Although dexmedetomidine was associated with reduced postoperative pain and improved sleep quality, it did not markedly prevent delirium. Therefore, identifying new anti-delirium agents and establishing evidence-based clinical guidelines remains critical.

Remimazolam, a novel ultrashort-acting benzodiazepine, primarily induces rapid sedation and anesthesia by selectively binding to GABAA receptors. Compared with traditional benzodiazepines, remimazolam offers a faster onset and shorter recovery time, providing clinical advantages (34,35). The pharmacological properties of remimazolam make it suitable for a range of clinical applications, including as a sedative and anti-epileptic medication. Remimazolam provides effective sedation without prolonging its duration of action, facilitating quicker recovery and earlier discharge of patients (35). In patients undergoing cardiac surgery, remimazolam has been shown to ensure good hemodynamic stability, with minimal impact on recovery and extubation times postoperatively (36). Wang *et al* (37) conducted a meta-analysis of randomized controlled trials, and the results suggested that remimazolam may be safer for elderly patients than other sedatives, as the

risk of POD following general anesthesia or sedation was not increased, and it may improve cognitive function after surgery. A recent randomized controlled trial also demonstrated that remimazolam, used in surgeries for lower extremity fractures in older adults, may increase the power spectrum density of the α band in frontal brain waves, thus improving postoperative cognitive function compared with midazolam (38). Furthermore, compared with other anesthetic agents such as propofol, remimazolam poses a lower risk of cardiovascular and respiratory depression (39).

In the present study, remimazolam significantly reduced anxiety scores, which may be attributed to its superior ability to alleviate pain and reduce inflammatory responses (40). Mao *et al* (41) similarly found that preoperative administration of remimazolam and estazolam, whether used individually or in combination, effectively eased preoperative anxiety during laparoscopic cholecystectomy. In the present study, the difference in anxiety scores between the two groups may be related to the differences in analgesic effects of different drugs. Patients with anxiety have a higher risk of developing POD after surgery (42). Gu *et al* (43) reported that the perioperative sleep quality of patients with preoperative anxiety was worse than that of patients without preoperative anxiety. Furthermore, high preoperative anxiety is related to more severe postoperative pain and an increased requirement for analgesia. Shimony *et al* (44) reported that perioperative use of twice-daily 150 mg pregabalin attenuated preoperative anxiety, improved sleep quality, and reduced postoperative pain scores and analgesic usage without increasing the rate of adverse effects, and indicated that anxiety may reduce the occurrence of POD. Ren *et al* (45) reported that preoperative anxiety may help to predict the risk of POD in elderly patients undergoing elective orthopedic surgery; therefore relieving preoperative anxiety could be a new target for preventive interventions to reduce POD. Given that the pharmacological profile of remimazolam reduces the likelihood of sedative-induced POD, this warrants attention for the potential of remimazolam in preventing and treating POD and postoperative anxiety.

Remimazolam has potential advantages in reducing the incidence of POD. Firstly, its effectiveness in preventing POD has been preliminarily established; a previous study comparing remimazolam to other anesthetic drugs, including propofol, in elderly patients found that the incidence of POD was significantly lower in those receiving remimazolam (6). Additionally, remimazolam has been shown to improve postoperative cognitive dysfunction, likely due to its anti-inflammatory and neuroprotective effects (46). Secondly, the pharmacological mechanism of remimazolam provides further theoretical support for its application in delirium prevention; research has indicated that remimazolam protects the nervous system by modulating neuroinflammatory responses and reducing the release of inflammatory factors, such as IL-6, IL-1β and tumor necrosis factor-α (46). Furthermore, remimazolam has been found to improve sleep patterns and reduce the incidence of postoperative sleep disorders, which are critical factors in preventing delirium (47). Finally, the safety and efficacy of remimazolam have been validated in clinical use. Compared with traditional anesthetics, remimazolam provides better hemodynamic stability and a lower incidence of adverse reactions (8). These characteristics position it as a promising agent for preventing delirium. Therefore, remimazolam holds considerable potential for POD prevention through mechanisms such as regulating neuroinflammation and improving sleep rhythms. However, further large-scale clinical trials are necessary to confirm its efficacy and safety.

The present study does have several limitations. It was a retrospective, single-center study, which inherently carries the risk of selection bias. Due to the substantial differences in treatment and sedation regimens in the control group, which could impact the results, future studies should aim for a uniform treatment regimen. Additionally, larger sample sizes are required to study POD more comprehensively, and large-scale, multi-center randomized controlled trials with expanded sample sizes are crucial for validation. We are currently registering and conducting a large sample size, multi-center randomized controlled trial study.

In conclusion, continuous intraoperative infusion of remimazolam may reduce the incidence of POD in elderly patients undergoing hip fracture surgery with subarachnoid block, likely due to its ability to alleviate intraoperative anxiety. Furthermore, remimazolam did not increase the incidence of perioperative complications; therefore, the clinical effects of remimazolam in preventing delirium are both safe and effective. However, further extensive multicenter randomized controlled trials are essential to substantiate these findings.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

QZ, LZ and BS contributed to the conception and design of the study. QZ and LZ were responsible for data collection and statistical analysis. QZ and BS wrote the initial draft of the manuscript. QZ revised the manuscript, managed the project, coordinated the study and provided final approval for the version to be published. All authors confirm the authenticity of all the raw data, contributed to manuscript revision, and read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by The Ethics Committee of the 904th Hospital of the Joint Logistics Support Force, People's Liberation Army of China (approval no. 2024-002) and was conducted in accordance with the principles set forth in The Declaration of Helsinki. Written informed consent was obtained from patients or their immediate family members.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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