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Remimazolam dosing for intraoperative sedation in elderly patients undergoing hip replacement with combined spinal-epidural anesthesia

Y. SONG, X.-J. ZOU

Department of Anesthesiology, Renhe Hospital Affiliated to Three Gorges University, Yichang City, Hubei Province, China

Abstract. – OBJECTIVE: The aim of the study was to investigate the 50% and 95% effective doses (ED50 and ED95) of remimazolam for intraoperative sedation in elderly patients undergoing hip replacement with combined spinal-epidural anesthesia (CSEA).

PATIENTS AND METHODS: We retrospectively analyzed the clinical data of 50 patients who underwent hip replacement with CSEA in our hospital from October 2021 to June 2022. There were 29 males and 21 females, aged 60-80 years old, with body mass indexes (BMI) ranging from 18 to 24 kg/m^2, and American Society of Anesthesiologists (ASA) classifications of I or II. The modified Dixon sequential method was used to determine the dose of remimazolam for each patient. Each patient's initial dose was 0.1 mg/kg/h, and the dose gradient was 0.01 mg/kg/h. The bispectral index (BIS) and the modified observer's assessment of alertness/sedation score (MOAA/S) were used to evaluate the sedation of the patient. An MOAA/S score ≤3 and a BIS <85 at three or more time points during surgery indicated the sedation was satisfactory. The induction dose of the next patient was adjusted by 0.01 mg/kg/h based on the level of sedation achieved, and the study was terminated after eight crossovers.

RESULTS: The ED50 and ED95 of remimazolam for sedation of elderly patients undergoing hip replacement with CSEA are 0.212 mg/kg/h (95% CI: 0.121-0.231 mg/kg/h) and 0.288 mg/kg/h (95% CI: 0.254-0.884 mg/kg/h), respectively. Two patients experienced transient bradycardia, five experienced hypoxemia, three experienced postoperative nausea, and three experienced postoperative delirium. No patients experienced adverse reactions such as injection pain, hypotension, vomiting, delayed awakening, or emergence agitation.

CONCLUSIONS: The ED50 and ED95 of remimazolam for sedation of elderly patients undergoing hip replacement with CSEA are 0.212 mg/kg/h and 0.288 mg/kg/h, respectively.

Key Words:
ED50, ED95, Remimazolam, Combined spinal-epidural anesthesia, Hip replacement.

Introduction

Hip replacement, also known as hip arthroplasty, is a widely performed orthopedic surgery for the management of a variety of hip joint disorders in elderly patients, such as rheumatoid arthritis, osteoarthritis, and osteonecrosis[1-4]. Elderly patients may live with various underlying diseases, such as increased sensitivity to anesthetics and decreased metabolism, and can be susceptible to anesthesia accumulation and poisoning[5]. These patients commonly experience adverse stress reactions and hemodynamic perturbations during the perioperative period[6]. The sedative agent for use in elderly patients should achieve intraoperative sedation while maintaining hemodynamic stability and respiratory function. Therefore, selecting a safe and effective sedative agent with the appropriate dosage is crucial to hip replacement success in elderly patients.

Remimazolam, an ultra-short-acting benzodiazepine sedative, is characterized by fast onset of action, rapid metabolism, context-sensitive half-life, and rapid elimination[7]. Compared with other sedative agents, such as midazolam and propofol, remimazolam has been shown to produce comparable anesthetic and analgesic effects in patients undergoing short surgical procedures. Moreover, remimazolam can alleviate the stress response while suppressing the respiratory and circulatory systems and is considered safe[8,9]. In recent years, remimazolam has gained popularity in the field of anesthesia for various surgical procedures, including gastroscopy, colonoscopy, hysteroscopy, and hip replacement[8,10-12]. Remimazolam is frequently administered in combination with regional anesthesia techniques to achieve a well-balanced anesthetic approach referred to as combined spinal-epidural anesthesia (CSEA). CSEA allows precise control of anesthesia and analgesia levels, making it a favorable option for procedures requiring varying degrees of sensory and motor blockade[13,14].

Corresponding Author: Xuejun Zou, MD; e-mail: zxj19740974@163.com

Despite the numerous studies[8,10-12,15] available on the efficacy and safety of remimazolam for sedation during various surgical procedures, there is a lack of studies specifically focusing on the optimal dosage of remimazolam in elderly patients undergoing hip replacement with CSEA. In this study, we aimed to fill this gap by exploring the 50% and 95% effective doses (ED50 and ED95) of remimazolam for sedation in elderly patients undergoing hip replacement with CSEA. These findings may provide a reference for the clinical use of remimazolam, leading to more standardized and evidence-based practices.

Patients and Methods

Patients

A retrospective analysis of 50 patients who underwent HR with CSEA in our hospital from October 2021 to June 2022 was conducted. There were 29 males and 21 females, aged 60-80 years old, with a body mass index (BMI) of 18-24 kg/m^2, and American Society of Anesthesiologists (ASA) classification of I or II. The study was approved by the Ethics Committee of Renhe Hospital Affiliated to Three Gorges University (No. 20220103), and patient consent was obtained for this retrospective study.

Inclusion Criteria

(1) Patients aged 60-80 years;
(2) Patients who met the indications for hip replacement and received hip replacement with CSEA[16];
(3) Patients with an ASA classification of I or II;
(4) Patients with preoperative Mini-Mental State Examination (MMSE) score ≥ 25;
(5) Patients with complete clinical data.

Exclusion Criteria

(1) Patients with cognitive impairment or mental illness;
(2) Patients with abnormal liver and kidney function;
(3) Patients with contraindications to surgery or anesthesia;
(4) Patients with a history of lower extremity nerve injury;
(5) Patients who had recently used narcotics.

Anesthesia Method

Preoperative protocol[17]

All patients were asked to fast for eight hours before the operation, and no preoperative medication was given. Heart rate (HR), electrocardiogram (ECG), oxygen saturation (SpO_2), blood pressure (BP), and bispectral index (BIS) were monitored before and during the operation. Oxygen was inhaled through the nasal catheter (2 L/min), and intravenous access was established. After local anesthesia, the left radial artery was punctured to monitor mean arterial pressure (MAP).

Anesthesia protocol[8]

The patients laid on their left side, the CSEA puncture was performed in the L3-L4 space, and 0.5% isogravity ropivacaine 10 mg (Qilu Pharmaceutical Co., Ltd., Jinan, Shandong, China). Specification (10 mL: 75 mg, Approval Number: H20052716) was injected slowly through the subarachnoid space. An epidural catheter was placed, and the position of the patient was adjusted to keep the anesthesia level controlled at T8. Remimazolam (Remimazolam Besylate for Injection, Yichang Renfu Pharmaceutical Co., Ltd., Yichang, Hubei, China. Approval Number: H20200006) was injected intravenously. The modified Dixon sequential method was used to determine the dose of remimazolam for each patient, with an initial dose of 0.1 mg/kg/h, and a dose gradient of 0.01 mg/kg/h. The BIS and the modified observer's assessment of alertness/sedation score (MOAA/S) were used to evaluate the sedation of the patient. An MOAA/S score ≤3 and a BIS <85 at three or more time points indicated satisfactory sedation. The induction dose of the following patient was adjusted by 0.01 mg/kg/h based on the level of sedation achieved. If the sedation was deemed unsatisfactory, the dose was decreased, and if sedation was satisfactory, the dose was increased. The study was terminated after eight crossovers, and the same anesthesiologist performed all the procedures above.

Management of adverse events[17]

If hypoxemia (SpO_2<90%) occurred during the operation, assisted ventilation was given to increase the inspired oxygen concentration and flow. When HR<50 times/min, an intravenous injection of 0.2-0.5 mg atropine was given. Conversely, when HR>90 times/min, an intravenous injection of 0.2-0.5 mg/kg esmolol was recommended. In cases in which the patient's SBP dropped > 20% from baseline or fell below 80 mmHg, intravenous ephedrine was given at a 6 mg/time dose to increase BP.

Observation Indicators

(1) HR, ECG, SpO_2, BP, BIS, MOAA/S, operation time, and recovery time of each patient were

recorded. Recovery time was defined as the time from the last intravenous injection of remimazolam to MOAA/S for three consecutive tests of five points each.

MOAA/S scoring criteria were as follows: 5 points, fully awake and normal response to name calling; 4 points, slow response to name calling; 3 points, only responds to loud and/or repeated name calling; 2 points, mild response to pushing or slight shaking of the body; 1 point, only responds to painful stimuli; 0 point, no response to painful stimuli[18].

(2) Adverse events, such as injection pain, nausea, vomiting, hypotension, bradycardia (HR<50 times/min), hypoxemia (SpO_2<90%), delayed awakening, emergence agitation, and postoperative delirium were recorded[19]. The presence of injection pain was determined by observing an escape reaction in the same limb after intravenous injection of remimazolam[19]. Nausea was assessed by the Numeric Rating Scale (NRS)[20]. The delirium status of the patients was assessed twice a day using the Confusion Assessment Method (CAM) scale for one week after surgery[21].

Statistical Analysis

Data analysis was performed using SPSS 23.0 (IBM Corp, Armonk, NY, USA). Measurement data were expressed as mean ± standard deviation. Probit regression analysis was used to calculate ED50, ED95 and 95% confidence interval (CI). GraphPad Prism 8 (GraphPad Prism, Inc., San Diego, CA, USA) was used to make sequential test diagrams of remimazolam sedation and fit the dose-response curves. p<0.05 indicated a statistically significant difference.

Table I. Baseline patient characteristics.

Characteristic	Number of patients (N=50)
Age, years, Mean (SD)	64.76±4.80
Sex, n (%)	
Male	29(58.00)
Female	21(42.00)
BMI, kg/m^2, Mean (SD)	21.72±1.41
ASA classification, n(%)	
ASA I	26(52.00)
ASA II	24(48.00)
Reasons for surgery, n(%)	
Femoral head necrosis	33(66.00)
Hip osteoarthritis	6(12.00)
Femoral neck fracture	11(22.00)
Operation duration, min, Mean (SD)	92.30±11.76

Results

Baseline Characteristics

A total of 50 patients were included in this study. There were 29 males and 21 females, with an average age of 64.76±4.80 years, and an average BMI of 21.72±1.41 kg/m^2. There were 27 cases of ASA class I and 23 cases of ASA class II (Table I).

Dixon Sequential Method

All patients underwent dose determination, with 29 patients (58%) achieving satisfactory sedation and 21 patients (42%) having unsatisfactory sedation. Figure 1 shows the sequential test chart of remimazolam sedation in elderly patients undergoing hip replacement with CSEA.

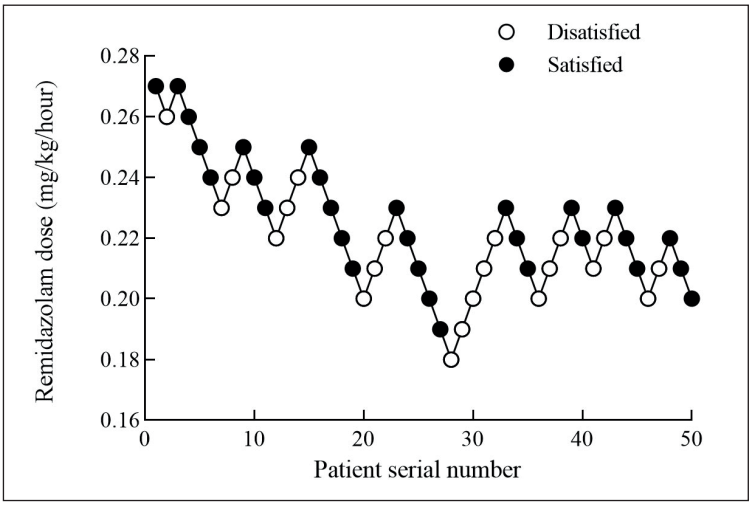

Figure 1. Sequential test diagrams of remimazolam sedation.

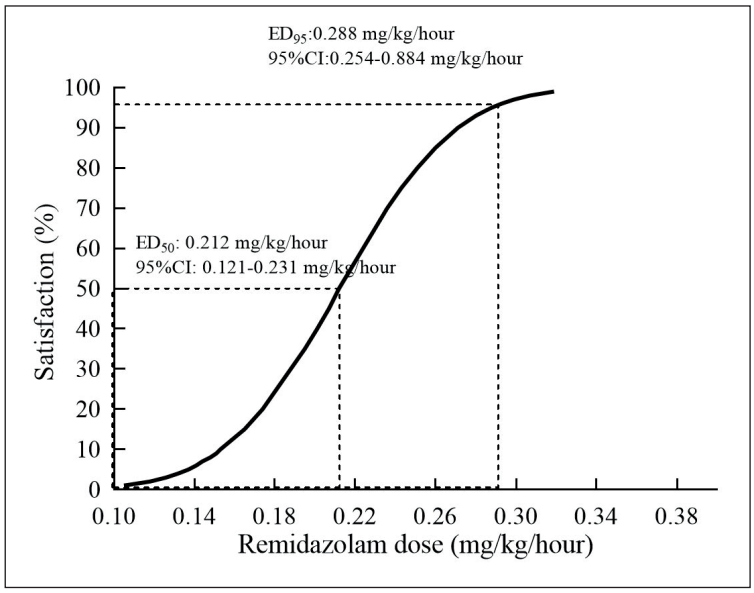

Figure 2. Dose-response curve of remimazolam sedation.

ED50 and ED95 of Remimazolam

Probit regression analysis showed that the ED50 and ED95 of remimazolam for sedation in elderly patients undergoing hip replacement with CSEA were 0.212 mg/kg/h (95%CI: 0.121-0.231 mg/kg/h) and 0.288 mg/kg/h (95 %CI: 0.254-0.884 mg/kg/h), respectively. Figure 2 depicts the dose-response curve.

Hemodynamic parameters and sedation depth assessment

HR and MAP 10 min, 30 min, and 60 min after sedation were significantly lower than before sedation ($p<0.05$), and HR and MAP 30 min and 60 min after sedation were significantly lower than 10 min after sedation (Table II; $p<0.05$). The MOAA/S score and BIS 10 min, 30 min, and 60 min after sedation were significantly lower than before sedation ($p<0.05$), and the MOAA/S score at 30 min and 60 min after sedation was significantly lower than 10 min after sedation (Table II; $p<0.05$).

Adverse events

There were two patients who experienced transient bradycardia, five patients who experienced hypoxemia, three patients who experienced postoperative nausea, and three patients who experienced postoperative delirium. No patients experienced adverse reactions of injection pain, hypotension, vomiting, delayed awakening, or emergence agitation (Table III).

Discussion

Remimazolam, a promising, rapidly metabolized benzodiazepine, has recently been approved for procedural sedation and general anesthesia[22]. Despite many studies on remimazolam[8,10-12,15], there is currently no consensus on the optimal sedative dose of remimazolam in elderly patients undergoing hip replacement. This study showed that remimazolam was an effective sedative agent

Table II. Hemodynamic parameters and sedation depth assessment at multiple time points.

Indicators	Before sedation	After sedation		
		10 min	30 min	60 min
Hemodynamic parameters				
HR (beats/min)	80.74±9.66	71.42±7.28[a]	64.96±5.31[a,b]	65.62±5.52[a,b]
MAP (mmHg)	97.5±10.4	94.00±11.41[a]	86.28±8.52[a,b]	87.84±8.52[a,b]
Sedation depth				
MOAA/S score	5 (5.5)	4 (3.4)[a]	3 (2.4)[a,b]	3 (2.4)[a,b]
BIS	94.26±6.85	78.96±6.21[a]	76.46±7.94[a]	76.78±7.63[a]

[a]$p < 0.05$, compared with before sedation; [b]$p < 0.05$, compared with 10 min after sedation.

Table III. Adverse events (n%).

Adverse events	Number of patients (N=50)
Transient bradycardia	2 (4.00)
Hypoxemia	5 (10.00)
Nausea	3 (6.00)
Postoperative delirium	3 (6.00)

for intraoperative use in elderly patients undergoing hip replacement with CSEA. We found that the ED50 and ED95 of remimazolam were 0.212 mg/kg/h and 0.288 mg/kg/h, respectively, with a high proportion of patients achieving adequate sedation and fewer adverse events.

In the present study, 29 (58%) patients had satisfactory sedation, which corresponded to the significantly lower HR, MAP, MOAA/S score, and BIS at various time points after sedation compared to before sedation and was consistent with previous findings[8]. Moreover, HR and MAP at 30 min and 60 min after sedation were significantly lower than HR and MAP at 10 min after sedation, as was the MOAA/S score, indicating that the doses of remimazolam used in this study were effective for sedation. Elderly patients require a sedative agent to have a fast onset of action, rapid distribution, short half-life, and fast metabolism. Remimazolam works by enhancing the binding of gamma-aminobutyric acid (GABA) to the GABA-A receptor, resulting in rapid action and distribution, suggesting it is an ideal sedative for elderly patients and can improve the safety of anesthesia[7].

The most common adverse events after intravenous remimazolam include hypotension, bradycardia, respiratory depression, hypoxia, injection pain, dizziness, nausea, and vomiting[7]. Severe bradycardia is not commonly reported in patients receiving remimazolam during surgery, and our results support this, as transient bradycardia was observed in two patients (4%)[23,24]. Both patients experienced an increase in HR after administration of atropine, which may support the concept that remimazolam is associated with better heart rate stability[25]. Hypoxemia occurred in five patients (10%), which differs from the results of Zhang et al[8] as hypoxemia was not reported in their study. Remimazolam may cause respiratory depression, even though there is a lower incidence of respiratory depression following sedation with remimazolam compared with other sedative agents[26]. Respiratory depression may result in a decrease in the amount of oxygen inhaled and an increase in the amount of carbon dioxide produced, which can reduce the amount of oxygen available to the body, leading to hypoxemia. Oxygen should therefore be administered routinely during sedation and close respiratory monitoring. Three patients experienced postoperative nausea but no vomiting in the study. The incidence of nausea and vomiting varied across studies, but most were low[8,27]. Remimazolam has a short half-life which means it is metabolized rapidly and accumulates less in the body, which can reduce the risk of nausea and vomiting. Postoperative delirium (POD) is a well-documented complication that occurs frequently in elderly patients who undergo surgery and anesthesia, with the incidence rate varying between 4%-65% across different surgical procedures[28]. Although benzodiazepines have been demonstrated to be a risk factor for POD, recent studies[29,30] have suggested that remimazolam is not significantly correlated with an elevated incidence of POD. This may be due to its rapid metabolism and non-accumulating properties, which may potentially contribute to the preservation of cognitive function in elderly patients. In this study, the incidence of POD (6%) was much lower than Yang et al[29] (15.6%) and Aoki et al[30] (30.3%). It is possible that the limited sample size of this study may be a reason for the different research outcomes observed. Patients did not experience any injection pain, hypotension, delayed awakening, or emergence agitation, suggesting that remimazolam has a good safety profile.

Limitations

There were some limitations associated with this study. As a retrospective study with small sample size, the generalization of the study results may be limited. The study focused primarily on elderly patients, and further research is needed to include younger individuals undergoing hip replacement. Finally, our study exclusively investigated elderly patients who received a hip replacement with CSEA, and more research is required to study the ED50 and ED95 of remimazolam for sedation in patients undergoing other surgical procedures.

Conclusions

The ED50 and ED95 of remimazolam for sedation in elderly patients undergoing hip replacement with CSEA were 0.212 mg/kg/h and 0.288 mg/kg/h, respectively. Remimazolam was found to be safe and effective in elderly patients undergoing hip replacement with CSEA.

Acknowledgment
The ED50 and ED95 of remimazolam for sedation in elderly patients undergoing hip replacement with CSEA were 0.212 mg/kg/h and 0.288 mg/kg/h, respectively. Remimazolam was found to be safe and effective in elderly patients undergoing hip replacement with CSEA.

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Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions
YS conceived and designed the study. YS and XZ collected the data and performed the literature search. YS was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

Ethical Approval and Patients Consent
The study was approved by the Ethics Committee of Renhe Hospital Affiliated to Three Gorges University (No. 20220103), and patient consent was obtained for this retrospective study.

Conflict of Interest
The authors declare that they have no conflict of interest.

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XZ: 0009-0009-9494-0899

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