Asploro Journal of Biomedical and Clinical Case Reports
(ISSN: 2582-0370)
Original Article
DOI: https://doi.org/10.36502/2024/ASJBCCR.6349

Comparison of Hepatic and Renal Functions during Intraoperative Sedation with Remimazolam in Elderly Patients under Intrathecal Anesthesia

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Received date: 14 May 2024; **Accepted date**: 29 May 2024; **Published date**: 05 June 2024

Citation: Zhao T. Comparison of Hepatic and Renal Functions during Intraoperative Sedation with Remimazolam in Elderly Patients under Intrathecal Anesthesia. Asp Biomed Clin Case Rep. 2024 Jun 05;7(2):131-35.

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Abstract

Background: Remimazolam mesylate for injection (RM) is a new benzodiazepine sedative drug. The aim of this trial was to evaluate the effects of drug metabolism on patients' hepatic and renal functions by comparing liver and renal function laboratory tests 24 hours before and 24 hours after surgery when using Remimazolam mesylate for injection (RM) for intraoperative sedation.

Methods: 40 surgical patients who underwent prostate electrocision under elective intrathecal anesthesia were included in this trial. Changes in the patients' perioperative hepatic and renal function indexes were analyzed using paired t-tests to assess the safety of Remimazolam mesylate for injection (RM) used for sedation in elderly patients under intrathecal anesthesia.

Results: The patients' preoperative 24-hour ALT (u/L) was 18.10 ± 4.97; the postoperative 24-hour ALT (u/L) was 18.08 ± 5.72; P = 0.975.

The preoperative 24-hour AST (u/L) was 18.83 ± 4.89; the postoperative 24-hour AST (u/L) was 19.73 ± 4.91; P = 0.358.

The preoperative 24-hour TBil (μmol/L) was 10.34 ± 6.16; the postoperative 24-hour TBil (μmol/L) was 12.03 ± 5.25; P = 0.008.

The preoperative 24-hour sCr (μmol/L) was 79.43 ± 26.31; the postoperative 24-hour sCr (μmol/L) was 71.80 ± 22.93; P = 0.001.

The preoperative 24-hour BUN (mmol/L) was 5.85 ± 1.75; the postoperative 24-hour BUN (mmol/L) was 4.83 ± 1.71; P < 0.001.

The preoperative 24-hour GFR (ml/min) was 82.73 ± 29.88; the postoperative 24-hour GFR (ml/min) was 125.23 ± 60.02; P < 0.001.

Important vital signs of the patients during the trial were stable, and laboratory tests of liver and renal function showed no abnormal changes of clinical significance.

Conclusion: The intraoperative vital signs of the patients were stable, and no significant adverse reactions were observed in liver and kidney functions when Remimazolam mesylate for injection (RM) was used for intrathecal anesthesia-assisted sedation in elderly patients.

Keywords

Remimazolam, Anesthesia, Sedation

Introduction

Remimazolam mesylate for injection (RM) is a new benzodiazepine sedative drug with a fast onset of action and short duration. It is metabolized by plasma cholinesterase, resulting in minimal impact on hepatic and renal function. Due to these properties, RM has been widely used in clinical anesthesia and sedation.

Elderly patients present specific challenges due to the decline of cardiorespiratory and neurological functions. These challenges include:

1. Decreased hepatic and renal functions and increased sensitivity to anesthesia drugs, which can lead to excessive sedation and significant changes in anesthesia monitoring indices.
2. Autonomic insufficiency and abnormal vascular elasticity and tone, which can cause cardiorespiratory, hepatic, and renal function abnormalities after sedation.

Therefore, the aim of our study was to observe the changes in perioperative hepatic and renal function in elderly male patients under sedation assisted by remimazolam mesylate (RM) for injection. We also sought to assess the safety of RM by monitoring commonly used clinical indices and laboratory test results [1-3].

Methods

Study Design and Patient Recruitment:

This trial was a single-arm, single-center, prospective clinical trial. Our trial was approved by the Ethics Committee of the Second Affiliated Hospital of Hainan Medical College (Approval number: reference number 2021-024-02, 20/5/2021) and registered on the official website of China Drug Clinical Trials (Registration number: ChiCTR2100051912, 9/10/2021). After obtaining ethical approval, we recruited patients who underwent elective prostatectomy under intrathecal anesthesia at the Second Affiliated Hospital of Hainan Medical College, and all patients signed an informed consent form. Recruited patients were aged 65-80 years old and were visited by an anesthesiologist one day prior to the surgery for a preoperative anesthesia assessment to determine eligibility for inclusion in the trial. The inclusion criteria were: ASA classification (American Society of Anesthesiologists physical status classification) of 1-2; BMI of 18-25 kg/m^2. The exclusion criteria were: patients with contraindications to intrathecal anesthesia, such as coagulation abnormalities, spinal structural abnormalities, puncture site infections, etc.; patients with established allergies to benzodiazepines; patients with difficult airways as assessed by the anesthesiologist; patients with diagnosed cardiopulmonary abnormalities, such as hypertension and coronary heart disease; patients with psychiatric diagnoses; patients with substance abuse issues (drug or alcohol); patients with hepatic and renal function abnormalities detected in laboratory tests; and patients with cardiac and pulmonary structural abnormalities detected by imaging. Exclusion criteria also included incomplete analgesia, high level of intrathecal anesthesia, and serious complications of intrathecal anesthesia, such as decreased blood pressure, slowed heart rate, and respiratory depression.

Perioperative Management:

On the day of surgery, the anesthesiologist performed pre-anesthesia preparation by checking the functionality of the anesthesia machine and monitor, as well as ensuring the BIS and EEG monitoring equipment were operational. The lumbar-rigid combined puncture kit was prepared. Remimazolam mesylate (RM) for injection was diluted with 0.9% sodium chloride to a concentration of 0.5 mg/ml. The medications used for lumbar-rigid combined anesthesia included 1% ropivacaine hydrochloride and 2% lidocaine hydrochloride. Emergency drugs, such as atropine sulfate injection and ephedrine hydrochloride injection, were prepared, and the benzodiazepine antagonist flumazenil was available if needed. Emergency endotracheal intubation and artificial ventilation devices were also prepared.

Before the patient entered the operating room, it

was ensured that the patient had not taken any sedatives or medications that could interfere with the procedure, anesthesia, or tests. The patient was required to fast for 8 hours or more. After confirming no abnormalities, the cardiac monitor was connected, peripheral venous access was opened, and an intravenous catheter was placed for sodium chloride infusion. The patient's vital signs, such as blood pressure, heart rate, and oxygen saturation, were observed. The patient inhaled room air throughout the procedure without additional oxygen. After 15 minutes of observation, if the patient's vital signs were stable, lumbar-hard joint anesthesia was administered.

Conduct of the Study:

The patient was placed in a lateral position with knees bent, and the anesthesiologist performed local anesthesia and puncture in the L3-L4 spinal space, using 2-3 ml of 2% lidocaine hydrochloride as a local anesthetic. Successful puncture was confirmed by the smooth flow of cerebrospinal fluid from the arachnoid puncture needle. After successful puncture, 0.5% ropivacaine hydrochloride (diluted with the patient's cerebrospinal fluid) was slowly injected. Following the injection, a catheter was inserted into the epidural cavity without injecting any drugs initially. After anesthesia was completed, the patient was returned to the supine position, and the anesthesia plane was evaluated using the Modified Bromage Scale (**Table-1**). 15 minutes later, the anesthesia plane was re-evaluated and, if it was fixed at a level no higher than T6 and no lower than T8, the patient was assisted into the lithotomy position in preparation for surgery. Mean arterial pressure (MAP), heart rate (HR), SpO_2, PVI, and other indicators of drug safety were recorded for a total of 10 minutes. After the recordings, patients received conventional surgical anesthesia as appropriate. The occurrence of adverse reactions to anesthesia was also recorded.

Table-1: Modified Bromage Scale

Score	Criteria
1	Complete block (unable to move knee or feet)
2	Almost complete block (able to move feet only)
3	Partial block (able to move knee only)
4	Detectable weakness of hip flexion while supine (full flexion of knee)
5	No detectable weakness of hip flexion while supine

Study Parameters:

Liver and renal function indexes, including ALT, AST, TBil, sCr, BUN, and GFR, measured 24 hours before and 24 hours after the operation, were used as indicators to evaluate the safety of Remimazolam mesylate (RM) for injection. Symptoms of adverse reactions, such as injection pain, nausea and vomiting, agitation, and delirium, were also recorded.

Study Outcomes:

The primary outcome of our trial was to evaluate drug safety by comparing changes in ALT, AST, TBil, sCr, BUN, GFR, and other indicators reflecting liver and kidney function before and after the use of RM.

Statistical Analysis:

Statistical analysis was performed using SPSS Statistics 25™ (SPSS Inc., Chicago, IL, U.S.A.). Values were expressed as the mean ± standard deviation (SD), mean (95% C.I.), or as numbers. A paired t-test was applied to analyze the changes in liver and kidney function before and after drug application. Statistical significance was defined by a P value < 0.05.

Results

During the course of the preoperative visit within 24 hours, as well as during the anesthesia procedure, 40 patients eventually completed our trial. Comparative data on the general condition of the final included patients are shown in **Table-2**.

Table-2: Demographic Characteristics of Patients

Characteristics	n=40
Age (year)	71.37±4.66
Height (cm)	160.75±6.37
Weight (kg)	57.98±6.49
BMI (kg/m2)	22.39±1.51

Discussion

In this single-arm, single-center, prospective clinical trial, we attempted to evaluate the effects on hepatic and renal function during metabolism of a novel benzodiazepine, remimazolam mesylate for injection (RM), by evaluating commonly used clinical markers of monitoring versus laboratory tests of hepatic and renal function.

Remimazolam mesylate for injection (RM) is a new type of benzodiazepine sedative drug, and with the rapid progress of its clinical application, its clinical indications have been gradually extended from intraoperative sedation for gastroenteroscopic surgery at the initial stage of marketing to the application of general anesthesia for tracheal intubation [4-6]. It takes effect in 1 minute, the blood concentration reaches its peak in about 3 minutes, and the MOAA/S score of patients reaches 4 or above in about 7 minutes, so it has a broad application prospect of intraoperative sedation. Meanwhile, it relies on plasma cholinesterase for metabolism, and has a slight effect on hepatic and renal functions. According to previous studies on the application of Remimazolam mesylate for injection (RM) in gastrointestinal endoscopic surgery, cardiac suppression and respiratory suppression were rare in patients, and thus it can be safely used in elderly patients. By studying the recommended dosage of remimazolam mesylate (RM) for injection at the initial stage of marketing and subsequent clinical studies in different centers, and combining with the conclusions of the previous clinical studies conducted in the Second Affiliated Hospital of Hainan Medical College, we chose 0.1 kg/mg as our test dose for the trial [7-9].

The liver and kidney function results 24 hours before and 24 hours after the operation are shown in **Table-3**. We observe no statistically significant difference between ALT, AST, and TBil, indicators of liver function tested before and after Remimazolam for Injection (RM) application ($P > 0.05$). However, there is a significant and statistically notable difference between TBil and RM ($P < 0.05$). Indicators assessing patients' renal function, including sCr, BUN, and GFR, exhibited statistically significant improvement ($P < 0.01$). Remimazolam mesylate for injection (RM) is metabolized by plasma cholinesterase, typically posing no additional burden on hepatic and renal functions. Nonetheless, previous studies referenced in our trial, along with the manufacturer's instructions, indicated some patients experienced an increase in blood bilirubin. In our cohort, the rise in blood bilirubin remained within the normal range. However, considering patients received perioperative antibiotics and other surgical drugs, we cannot dismiss the possibility of drug correlation influencing bilirubin metabolism. While renal function tended to improve, TURP's alleviation of urinary obstruction symptoms makes it difficult to accurately assess the effect of remimazolam mesylate (RM) for injection on renal function. Nevertheless, our findings indicate RM for injection maintains a high degree of safety and controllability in intraoperative sedation.

There are aspects of our experiment requiring improvement, notably in sample size analysis. Our trial, being single-center and single-arm, would have benefited from a larger participant pool for a more accurate analysis of individual patient differences.

Conclusion

Remimazolam mesylate for injection (RM) was used for intravertebral anesthesia-assisted sedation in elderly patients when the patient's intraoperative vital signs were stable, and no significant adverse reactions were seen in liver or kidney function.

Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

Table-3: Laboratory Tests of the Patient's Liver and Kidney Function

Characteristics	24 hours before surgery (n=40)	24 hours after surgery (n=40)	*P* value
ALT (u/L)	18.10 ± 4.97	18.08 ± 5.72	*P = 0.975*
AST (u/L)	18.83 ± 4.89	19.73 ± 4.91	*P = 0.358*
TBil (μmol/L)	10.34 ± 6.16	12.03 ± 5.25	*P= 0.008*
sCr (μmol/L)	79.43 ± 26.31	71.80 ± 22.93	*P = 0.001*
BUN (mmol/L)	5.85 ± 1.75	4.83 ± 1.71	*P < 0.001*
GFR (ml/min)	82.73 ± 29.88	125.23 ± 60.02	*P < 0.001*

Funding

There was no funding received for this paper.

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