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Effects of Esketamine on Postoperative Depression in Elderly Patients Undergoing Joint Replacement

Li Mao

Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan, 637000, China

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Abstract: This study aims to evaluate the effects of esketamine on postoperative depressive symptoms in elderly patients undergoing joint replacement surgery. Sixty elderly patients scheduled for unilateral total hip or knee replacement were included in the study and randomly divided into two groups using a random number table: the esketamine group (Group A, n=30) and the control group (Group D, n=30). Patients in Group A received intravenous infusion of 0.5 mg/kg esketamine during surgery, while those in Group D were given an equal amount of saline as a control. After surgery, they were connected to a patient-controlled analgesic pump. Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA) scores were assessed and recorded preoperatively, 3 days postoperatively, and 7 days postoperatively. Visual Analog Scale (VAS) scores were also assessed and recorded at 1 day, 3 days, and 7 days postoperatively. Adverse reactions during and after surgery were recorded. At 3 days and 7 days postoperatively, the HAMD and HAMA scores in Group A were significantly lower than those in Group D ($P<0.05$). However, there was no significant difference between the two groups in terms of VAS scores or the incidence of postoperative adverse reactions. A dose of 0.5 mg/kg esketamine can effectively improve postoperative depressive and anxiety symptoms in elderly patients undergoing joint replacement surgery without increasing the incidence of postoperative adverse reactions

1. Introduction

Osteoarthritis of the hip joint, hip fractures, avascular necrosis of the femoral head, osteoarthritis of the knee joint, and rheumatoid arthritis are relatively common in elderly patients. When conservative treatments prove ineffective, total joint replacement surgery becomes the preferred treatment option. With the intensification of population aging in China, the number of elderly patients undergoing joint replacement surgery is increasing, and these patients often have multiple underlying conditions, with lower pain tolerance [1]. Anxiety and depression are common adverse emotions during the perioperative period for joint replacement patients, significantly impacting postoperative recovery [2]. Escalcine is the racemic form of ketamine, with higher affinity for N-methyl-D-aspartate (N-methyl-D-aspartic acid receptor, NMDA) receptors, thus exhibiting stronger sedative, analgesic, and antidepressant effects, with milder side effects [3]. Therefore, we conducted this study to investigate the impact of escalcine on postoperative depression in elderly patients undergoing joint replacement surgery.

2. Data and Methods

2.1 General Information

This study included 60 elderly patients who underwent unilateral joint replacement surgery using subarachnoid block at the Affiliated Hospital of North Sichuan Medical College from March 2023 to February 2024. Inclusion criteria were: age 65 to 80 years, undergoing total hip or total knee replacement, and American Society of Anesthesiologists (American Society of Anesthesiologists, ASA) classification II-III. Exclusion criteria included: allergy to anesthetic drugs, severe hypertension (BP ≥ 180/100 mmHg), significantly elevated intraocular pressure, unstable angina or myocardial infarction within 6 months, alcoholism or drug abuse, history of neurological or psychiatric disorders, and contraindications for spinal anesthesia. The exclusion criterion was surgery duration exceeding 180 minutes. This study has been approved by the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (Ethical Number: 2023ER035-1), and patients or their families have signed informed consent forms.

2.2 Grouping and Treatment

According to the random number table method, patients were divided into the esketamine group (Group A, n=30) and the control group (Group D, n=30). Patients fasted for 8 hours and abstained from drinking for 2 hours before surgery. Upon entering the operating room, an upper limb venous access was opened, and routine monitoring of electrocardiogram (ECG), non-invasive blood pressure (NBP), and pulse oximetry (SpO_2) was performed. The patients were placed in a lateral position, and a subarachnoid injection of 0.75% bupivacaine 1.5ml was administered at the L2-L3 or L3-L4 intervertebral space, adjusting the anesthesia level to T6-T10. Before the start of surgery, Group A received 0.5 mg/kg of esketamine, diluted to 20ml and administered via intravenous pump for 30 minutes; Group D received an equal amount of 0.9% normal saline. After surgery, the analgesic pump was connected to the venous access. The analgesic pump formula for Group A was: tropisetron 10 mg, butorphanol 8 mg, sufentanil 200 μg, and esketamine 0.5 mg/kg, diluted to 150ml with normal saline; the formula for Group D was: tropisetron 10 mg, butorphanol 8 mg, and sufentanil 200 μg, diluted to 150ml with normal saline. The analgesic pump settings were background rate of 2.5 ml/h, hold time of 15 minutes, and single dose of 1 ml. If postoperative VAS pain score was ≥4 and the analgesic effect was poor, tramadol 0.1g was administered intramuscularly for rescue analgesia.

2.3 Observation Indicators

Researchers should evaluate and record the Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA) scores at preoperative (T0), three days postoperative (T3), and seven days postoperative (T7). Additionally, medical staff must record the visual analog pain scale (VAS) scores on postoperative day 1 (T1), three days (T3), and seven days (T7). Furthermore, clinicians are required to assess and document the occurrence of adverse reactions, including postoperative skin itching, dizziness, nausea and vomiting, and vivid dreams.

2.4 Statistical Analysis

Data analysis was conducted using SPSS 20 software. For measurement data that follow a normal distribution, mean ± standard deviation ($x \pm s$) is used, and independent samples t-tests are employed for inter-group comparisons. If the measurement data do not conform to a normal

distribution, median (M) and interquartile range (IQR) are used, and Mann-Whitney U tests (rank-sum tests) are applied for inter-group comparisons. Categorical data are expressed as percentages (%), and χ-tests (χ^2-tests) are used for inter-group comparisons. A P-value <0.05 is considered statistically significant.

3. Results

In this study, 66 cases were initially included, with 33 cases in each group. In Group A, 1 case was changed to general anesthesia due to insufficient anesthesia plane, and 2 cases were lost to follow-up after surgery; in Group D, 1 case was excluded because the operation time exceeded 180 minutes, and 2 cases were lost to follow-up after surgery. Finally, 60 cases were included, with 30 cases in each group.

3.1 Comparison of General Patient Data

There were no significant differences in age, gender distribution, ASA classification, body mass index (BMI), type of surgery, duration of surgery and intraoperative bleeding (P>0.05).

3.2 Comparison of Hamilton Depression Scale scores

Compared with group D, the HAMD score of group A decreased significantly at 3 days (T3) and 7 days (T7) after surgery (P<0.05), but there was no significant difference in the preoperative (T0) score between the two groups (P>0.05), as shown in Table 1.

Table 1 Comparison of HAMD scores at different time points in two $\bar{x} \pm s$ groups of patients (points)

metric	group	Examples	T0	T3	T7
HAMD score (points)	A group	30	9.4±2.9	7.1±1.2a	5.6±1.0a
HAMD score (points)	D group	30	9.1±2.8	8.4±2.1	8.1±1.4

Note: Compared with group D, aP <0.05.

3.3 Comparison of Hamilton Anxiety Scale Scores

The HAMA score of group A was significantly lower than that of Group D at 3 days (T3) and 7 days (T7) after surgery (P<0.05), but there was no significant difference in the preoperative (T0) score between the two groups (P>0.05), as shown in Table 2.

Table 2 Comparison of HAMA scores at different time points in two $\bar{x} \pm s$ groups of patients (points)

metric	group	Examples	T0	T3	T7
HAMA score (points)	A group	30	9.1±2.4	7.1±1.1a	5.5±0.7a
HAMA score (points)	D group	30	9.2±2.1	8.3±0.9	6.8±0.8

Note: Compared with group D, aP <0.05.

3.4 Comparison of Postoperative VAS Scores

The VAS scores of group A were lower than those of Group D on day 1 (T1),3 (T3) and 7 (T7) after surgery, but there was no significant difference between the two groups (P>0.05), as shown in Table 3.

Table 3 Comparison of VAS scores at different time points between the two $\bar{x} \pm s$ groups (points)

metric	group	Examples	T1	T3	T7
VAS grade	A group	30	2.9±0.4	2.2±0.4	1.3±0.5
VAS grade	D group	30	3.1±0.5	2.3±0.5	1.6±0.5

3.5 Comparison of Postoperative Adverse Reactions Between the Two Groups

There was no statistically significant difference in the incidence of postoperative skin itching, dizziness, nausea and vomiting, and vivid dreams between the two groups (P>0.05). Group A had 4 cases of skin itching, while Group D had 2 cases; Group A had 5 cases of dizziness, while Group D had 3 cases; Group A had 5 cases of nausea and vomiting, while Group D had 3 cases; Group A had 8 cases of vivid dreams, while Group D had 5 cases. Neither Group A nor Group D reported any nightmares.

4. Discussion

Elderly patients, due to the imbalance of calcium and phosphorus metabolism in bones and degenerative changes in bone structure, are prone to various bone and joint diseases, with hip and knee arthritis being the most common. These degenerative conditions not only severely impact the quality of daily life but also often require further artificial joint replacement surgery to improve function and alleviate pain when conservative treatments prove ineffective. It is worth noting that elderly patients frequently suffer from multiple underlying conditions, such as cardiovascular disease and diabetes. Long-term chronic pain and mobility issues can trigger a series of psychological stress responses, including perioperative anxiety and depression. Depression not only affects the patient's quality of life but can also lead to an increase in postoperative complications, prolong hospital stays, and higher medical costs. Therefore, preventing and treating postoperative depression is crucial for the rehabilitation of elderly patients. Doctors often focus on pain while neglecting negative emotions, making drugs that can both relieve pain and alleviate negative emotions essential. Ketamine, as a novel anesthetic adjunct, has gained significant attention due to its unique pharmacological properties. As the racemic form of ketamine, esketamine primarily exerts its pharmacological effects by acting on NMDA receptors, inhibiting glutamate release, thereby producing sedative, analgesic, and antidepressant effects. NMDA receptors are widely distributed in the central nervous system and play a role in regulating multiple neurotransmitters, particularly in pain and mood regulation. By acting on NMDA receptors and inhibiting glutamate release, esketamine reduces neuronal hyperexcitability, thus achieving analgesic and antidepressant effects. In addition, esketamine can further improve depressive symptoms by promoting the release of brain-derived neurotrophic factor and enhancing neural plasticity. In recent years, the application of esketamine in perioperative period has gradually become a research hotspot, especially showing great potential in improving postoperative pain management and alleviating psychological stress response.

This study explored the application value of esketamine in perioperative care for elderly patients undergoing joint replacement surgery through a randomized controlled clinical trial design. The results showed that the use of esketamine during and after surgery significantly reduced the HAMD depression scores at 3 and 7 days postoperatively, indicating its significant clinical effect in improving perioperative depressive symptoms. Luo et al. found in a randomized controlled trial that 0.5 mg/kg of esketamine demonstrated a significant advantage in alleviating postoperative depressive symptoms [4], further confirming the potential value of esketamine in perioperative antidepressant treatment. Additionally, this study observed a significant improvement in

postoperative anxiety symptoms with esketamine. The Hamilton Anxiety Rating Scale scores at 3 and 7 days postoperatively were significantly lower in the esketamine group compared to the control group, which may be related to its inhibitory effect on NMDA receptors in γ-aminobutyric acid (GABA) interneurons. By inhibiting these receptors, esketamine promotes glutamate release, thereby enhancing nervous system excitability and effectively alleviating anxiety symptoms [5]. This mechanism provides a theoretical basis for the application of esketamine in perioperative anxiety management.

In this study, the Hamilton Depression Rating Scale and the Hamilton Anxiety Rating Scale were selected to assess patients 'depressive and anxious states. The Hamilton Depression Rating Scale is one of the widely used tools for depression assessment in clinical practice. Its advantage lies in its structured and systematic design, which can comprehensively evaluate the severity of depressive symptoms. HAMD includes 17 or 21 items, covering multiple dimensions such as mood, physical symptoms, and cognitive function, making it highly practical and operational in clinical settings. Its scoring criteria are clear, facilitating rapid assessment of patients' depressive status by doctors in clinical practice, especially suitable for evaluating severe depression. Additionally, HAMD is also widely used in research due to its ability to quantify changes in depressive symptoms, aiding in efficacy evaluation and long-term follow-up. In contrast, other depression rating scales like the Beck Depression Inventory and the Patient Health Questionnaire have their own advantages. The Beck Depression Inventory is a self-rating scale that reflects the patient's subjective feelings, suitable for screening mild to moderate depression. The Patient Health Questionnaire is known for its simplicity and efficiency, making it appropriate for primary care and community healthcare. However, these scales have the disadvantage of having a narrower coverage, possibly failing to fully reflect the complex symptoms of severe depression. Therefore, this study chose the Hamilton Depression Rating Scale to assess patients' depressive state. The Hamilton Anxiety Rating Scale is a classic tool for assessing the severity of anxiety symptoms, with its advantage being its structured and multidimensional design, covering both mental and physical anxiety symptoms, consisting of 14 items, which can comprehensively reflect the patient's anxious state. HAMA is widely used in clinical and research settings, particularly for the quantitative analysis of generalized anxiety disorder and drug efficacy. Its scoring criteria are clear, making it easy for doctors to use, and it has high reliability and validity. In comparison, other anxiety scales such as the Generalized Anxiety Disorder Scale and the Beck Anxiety Inventory have their own advantages. The Generalized Anxiety Disorder Scale is concise and efficient, suitable for primary care screening; the Beck Anxiety Inventory focuses on the patient's self-reported experience, reflecting subjective anxiety. However, these scales have a narrower coverage and may not comprehensively assess complex anxiety symptoms. Therefore, this study chose the Hamilton Anxiety Rating Scale. In terms of safety, this study meticulously documented and analyzed postoperative adverse reactions in both groups of patients. The results showed no significant difference in the incidence of common postoperative adverse reactions between the two groups. Group A had 5 cases of nausea and vomiting, while Group D had 3 cases; Group A had 4 cases of skin itching, while Group D had 2 cases; Group A had 5 cases of dizziness, while Group D had 3 cases; Group A had 8 cases of vivid dreams, while Group D had 5 cases. Neither group reported any nightmares. Although the incidence of adverse reactions in Group A was higher than in Group D, there was no statistically significant difference between the two groups. This result indicates that the use of esketamine perioperatively did not increase the risk of perioperative adverse reactions, and its safety has been preliminarily verified in clinical applications. However, potential side effects such as hallucinations, nausea, and vomiting should still be noted, especially with long-term or high-dose use. Therefore, in clinical practice, the indications and dosage should be strictly controlled to ensure patient safety.

However, this study also has some limitations. First, the sample size is small, and future research

should expand the sample size and conduct multicenter studies. Second, this study only targeted elderly patients, making it impossible to determine the impact of esketamine on perioperative depression in young and middle-aged patients. Finally, the observation period was relatively short, with a maximum duration of only 7 days, and further research is needed to assess the antidepressant effects over longer periods, such as 1 month, 6 months, and 12 months.

In conclusion, in elderly patients undergoing joint replacement, esketamine at a dose of 0.5mg/kg can significantly improve postoperative depression and anxiety without increasing the incidence of postoperative adverse reactions, showing good clinical application prospects.

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