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Effect of esketamine on postoperative sleep disturbance in patients undergoing spinal surgery: a study protocol for a randomized, double-blinded, placebo-controlled clinical trial

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Abstract

Introduction： Postoperative sleep disturbance (PSD) is a common complication after spinal surgery that can be related to postsurgical pain, perioperative anxiety and depression. Recent studies have shown that esketamine may improve sleep disturbance after surgery; however, it remains unclear whether intraoperative infusion of esketamine can improve the postoperative sleep quality of patients undergoing spinal surgery.

Methods： This is a protocol for a randomized, double-blinded, placebo-controlled clinical trial to evaluate the effect of esketamine on PSD in patients undergoing spinal surgery. Patients aged 18 to 65 years who plan to undergo selective spinal surgery will be randomly allocated to the esketamine group or control group at a ratio of 1:1. Esketamine or saline will be infused at the same speed of 0.3 mg/kg/h during the surgery by the anaesthesiologists in charge who are blinded to the randomization. The primary outcome of the study was the incidence of postoperative sleep disturbance (PSD) during the first 3 days after surgery. The secondary outcomes included objective sleep quality, NRS scores and Hospital Anxiety and Depression Scale (HADS) scores.

Ethics and Dissemination： The study was approved by the Ethical Committee of Beijing Tiantan Hospital, Capital Medical University (KY2024-013-02). The study was registered on clincaltrials. gov on June 4,2024 (NCT 06451627). Our study might guide perioperative anaesthesia management plans and improve PSD in patients undergoing spinal surgery. The findings of the study will be published in peer-reviewed journals and will be presented at national or international conferences.

Trial registration: ClinicalTrials.gov Identifier: NCT 06451627

Keywords: Esketamine, Postoperative sleep disturbance, Spinal surgery

Strengths and limitations of this study

- Postoperative sleep disturbance (PSD) is one of the most common complications after spinal surgery with high incidence. However, clinical treatments considered to improve PSD remain insufficient.
- Esketamine is a right-handed monomer of ketamine that retains all the advantages of ketamine and has a stronger affinity for NMDA receptors. Recently, there has been increasing interest in its ability to improve sleep disturbance because of its anti-inflammatory, powerful analgesic and antidepressant effects.
- This study is a randomized controlled trial to evaluate the effect of esketamine on the PSD of patients undergoing spinal surgery. The safety of intraoperative esketamine infusion at a speed of 0.3 mg/kg/h during surgery will also be examined.

Introduction

Postoperative sleep disturbance (PSD), which can result in sleep fragmentation, deprivation, and a reduction in slow-wave sleep (SWS) and rapid eye movement (REM) sleep, is one of the most common complications after major surgery, and its incidence varies from 30-80%[1,2]. The incidence of PSD after spinal surgery is approximately 61.4%.[3] Previous investigations have reported that continued PSD can cause chronic pain or increased pain sensitivity, heightened stress levels, delirium, gastrointestinal dysfunction, increased risk of cardiovascular events and decreased immune responses[4 2,5]. Therefore, sleep promotion is one of the most important ways to help surgical patients recover by reducing delirium, pain, fatigue, and cognitive dysfunction.

PSD is associated with factors such as the type of anaesthesia, postoperative pain, the ward environment, and psychological factors such as preoperative anxiety or depression[6]. Currently, clinical treatments considered to improve PSD include enhanced analgesia and nonpharmacological [7] and pharmacological interventions[8] (such as melatonin). Inadequate pain control, which remains a main problem for postoperative management, can impact patients' sleep and rehabilitation to a large extent[4]. Opioids are commonly used for postoperative analgesia after spinal surgery; however, they do not improve but rather worsen postoperative sleep by decreasing the duration of rapid eye movement (REM) sleep and nonrapid eye movement (NREM) stage 3 sleep and increasing the apnea-hypopnea index (AHI)[9]. Therefore, it is necessary to consider other analgesics and administer multimodal analgesia.

Ketamine, an N-methyl-D-aspartate receptor antagonist, is the only intravenous anaesthetic drug that has both sedative and analgesic effects. Esketamine is a right-handed monomer of ketamine that retains all the advantages of ketamine and has a stronger affinity for NMDA receptors. A meta-analysis[10] showed that esketamine can assist in analgesia and decrease the intensity of pain within 24 h after surgery, as well as reduce the total dosage of opioid analgesics. In addition, previous studies reported that subanaesthetic doses (0.2 and 0.4 mg/kg, intravenously) of esketamine have a rapid and powerful therapeutic effect on

patients with treatment-resistant depression[11]. Recently, there has been increasing interest in its ability to improve sleep disturbance because of its anti-inflammatory, powerful analgesic and antidepressant effects[12]. In addition, esketamine may affect circadian genes to regulate sleep-wake and circadian systems[13]. Duncan et al. reported that ketamine may act on clock-related molecules and brain-derived neurotrophic factor (BDNF) levels, leading to alterations in the circadian rhythm of the central clock; increasing total sleep, rapid eye movement (REM) sleep, and slow-wave sleep; and improving sleep quality in patients with treatment-resistant depression[14]. Initial studies have shown that intraoperative and postoperative infusion of esketamine can improve PSD[15] in patients after gynecological laparoscopy. However, only a few high-quality clinical studies have confirmed the effect of esketamine on PSD in surgical patients.

Since research on the effect of esketamine on PSD in patients undergoing major spinal surgery is scarce and objective measures of sleep are lacking[15], we conducted this randomized, double-blinded, placebo-controlled clinical trial. The primary outcome was the incidence of PSD, defined as an Athens Insomnia Scale (AIS) score of 6 points or higher on the night after surgery. We will also perform objective monitoring of postoperative sleep as a secondary outcome.

Methods/design

Study design

This study is a prospective, single-center, randomized, double-blinded, placebo-controlled clinical trial that will be carried out at Beijing Tiantan Hospital, Capital Medical University. The trial was approved by the Institutional Review Board of Beijing Tiantan Hospital (KY2024-013-02) and registered at ClinicalTrials.gov (NCT 06451627) on June 4,2024. All participants or their legal representatives signed informed consent after screening and before randomization.

Participant recruitment

Inclusion criteria

1. Aged 18 to 65 years.
2. American Society of Anesthesiologist Physical Status classification of I to III.
3. The patient underwent elective spinal surgery under general anaesthesia.
4. Signed informed consent.

Exclusion criteria

1. Body mass index (BMI) ≥35 kg/m^2.
2. Severe lesions of important organs.
3. The patient underwent tracheal intubation or was admitted to the intensive care unit (ICU) postoperatively.
4. History of adverse reactions or contraindications to ketamine or esketamine.
5. Cognitive dysfunction, communication disorders.
6. Patients who refused to participate in this study.

Randomization and blinding

All patients scheduled for spinal surgery will be screened 2 days before surgery for eligibility. They will be informed about the aims, procedures, benefits, possible risks of study and how to react if risks occur. Written informed consent will be obtained during preoperative evaluation by an anesthesiologist. Subsequently, each patient will be randomly allocated to either the esketamine group or the control group at a 1:1 ratio using a variable block randomization method. All study-related investigators will be blinded to the randomization results.

Dispensing and labelling of the study drugs will be performed by an independent nurse. Esketamine (Hengrui Induction, Jiangsu, China) will be diluted to a concentration of 1 mg/mL with normal saline. Both esketamine and normal saline will be kept in syringes (50 mL) with the same appearance and labelled with 'the trial drugs, randomization code'. The trial drug will be given to the participants at a speed of 0.3 mL/kg/h during the surgery. The labelled syringes will be distributed to the attending anesthesiologists responsible for anaesthetic management after induction. The anaesthesiologists, accessors and patients will be blinded to the type of drug administered until the final statistical analyses are completed. The administered drug will be unmasked during medical treatment when severe adverse events related to esketamine occur, with the agreement of the primary investigator.

Anaesthesia management

Standard ASA parameters, including blood pressure, electrocardiogram, pulse oxygen saturation, body temperature, and end-tidal carbon dioxide partial pressure ($ETCO_2$), will be monitored perioperatively. Anaesthesia induction will be conducted with 1-2 mg/kg propofol or 0.3 mg/kg etomidate, 0.2-0.4 μg/kg sufentanil and 0.6 mg/kg rocuronium or 0.1-0.15 mg/kg cisatracurium. Total intravenous anaesthesia with propofol, remifentanil and the 'trial drug' will be implemented for anaesthesia maintenance based on the bispectral index (BIS) and maintained between 40 and 60. The surgeon performed wound infiltration with 20 mL of 0.5% ropivacaine after the last suture.

Patient-controlled analgesia (PCA) devices will be applied after surgery by using sufentanil (2 μg/kg) and ondansetron (16 mg) in a total volume of 100 ml to maintain NRS scores equal to or less than 4. The device is programmed to administer a background dose of 2 mL/hour, as well as a bolus dose of 0.5 mL with a lockout interval of 15 min for 48 hours. Other analgesics could be used for rescue therapy for severe pain (numerical rating scale score greater than 4) during the postoperative period and should be recorded.

Outcomes

The primary outcome of the study was the incidence of PSD during the first 3

days after surgery, which was evaluated by the Athens Insomnia Scale (AIS) on the morning (8-10 am) of postoperative days 1-3, and a score of 6 or higher was defined as PSD.

The secondary outcomes included the following:

1. Objective sleeping quality will be assessed with a wristwatch (Huawei Watch GT3pro, Huawei Technologies Co., Ltd., Shenzhen, China) on the first and third nights after surgery. The wristwatch connects to a mobile app via Bluetooth and generates a sleep report that covers total sleep time, light sleep time, deep sleep time, the number of awakenings and so on.

2. Postoperative pain assessment: Postoperative pain at rest and during movement will be evaluated on the morning (8-10 am) of postoperative days 1-3 using an 11-point NRS (0 indicating no pain, 10 indicating the worst pain imaginable). The analgesic consumption and supplemental analgesic use within 72 h will also be recorded.

3. Postoperative anxiety and depression assessment: Postoperative anxiety and depression scores will be measured by the Hospital Anxiety and Depression Scale. On the morning (8-10 am) of postoperative days (PODs) 1 and 3, a score of 8 points or higher indicated depression or anxiety.

Safety outcomes will include all drug-related adverse events, including bradycardia, hypotension, tachycardia, hypertension, arrhythmia, nystagmus, hypersalivation, euphoria, emergence agitation, hallucinations, dreaminess and nightmares during surgery or before discharge. Patients will be followed up for 3 consecutive days (at 8-10 am).

Data management

All paper versions of the original materials, including the protocol, case report forms, and informed consent forms, will be photographed and saved in an encrypted database. All electronic data will be stored in the electronic medical records of Beijing Tiantan Hospital. All procedures for evaluating endpoints will be filmed and saved**.**

Sample size calculation

The PASS 15 software (NCSS, LLC, USA) was used to calculate the sample size based on the primary endpoint. According to our preliminary study, the incidence of PSD after spinal surgery is approximately 60%, and we hypothesize that the incidence of PSD will decrease by 50% after esketamine infusion. Taking this into account, the sample size in each group should be seventy-eight to achieve a power of 80% at a two-tailed significance level of 0.05, with a drop-out rate of 10%.

Statistical analysis

The statistical analysis will be performed by an independent statistician using SPSS 25.0 (Somers, NY, USA). The data will be analysed on a per protocol basis. Descriptive statistics of all variables describing the characteristics of the patients enrolled in the study and those excluded from the study will be analysed. All measurement data were analysed for a normal distribution and homogeneity of variance. Normally distributed data are presented as the means ± SDs. Nonnormally distributed data will be presented as medians. Categorical variables will be summarized as percentages and numbers of patients.

The primary endpoint of the incidence of PSD during the first 3 days will be analysed using the $\chi 2$ test or Fisher's exact test. The secondary outcomes will be analysed using t tests, Mann–Whitney U tests and $\chi 2$ or Fisher's exact tests, as appropriate. A logistic regression model was used to assess the potential risk factors associated with PSD. A two-sided *P* value of less than 0.05 was considered to indicate statistical significance. No interim analysis will be performed, and the study will be terminated after enrollment of the last patient.

Reporting of adverse events

All adverse events associated with this trial will be recorded in detail and closely monitored until resolution or stabilization or until it has been shown that study treatment is not the cause of the event. The principal investigator will be responsible for reporting all adverse events. Once adverse events occur, they should be immediately reported to the ethics committee within 24 hours and informed to the principal investigator to determine the severity of the adverse events.

Patient and Public Involvement

Patients and the public were not involved in the trial design. Participants will have access to the findings of the study on request.

Ethics and dissemination

Approval for the study was provided by the Ethical Committee of Beijing Tiantan Hospital, Capital Medical University (KY2024-013-02). The study was registered on clincaltrials.gov on June 4, 2024. The findings of the study will be published in peer-reviewed journals and will be presented at national or international conferences.

Discussion

This study explored the efficacy and safety of intraoperative esketamine infusion on PSD in patients undergoing elective spinal surgery with general anaesthesia. Participants will receive either esketamine or saline infusion at a speed of 0.3 mg/kg/h during the surgery. Moreover, propofol and remifentanil were implemented for anaesthesia maintenance based on the BIS, and the BIS was maintained between 40 and 60. Both subjective and objective sleep measures will be assessed after surgery. The adverse events will also be observed and reported.

Pain is a main cause of PSD in surgical patients and can prolong sleep latency and reduce total sleep time[4]. However, it is extremely difficult to manage postoperative pain in patients undergoing orthopedic surgery, especially spinal surgery. Opioids, commonly used clinical analgesics, have many adverse effects, including respiratory depression, nausea, vomiting, and postoperative hyperalgesia, and can also cause PSD characterized by a reduced duration of slow-wave sleep, rapid eye movement (REM) suppression, and increased duration of arousal [20]. Therefore, multimodal analgesia can better control postoperative pain through nerve blockade and the use of nonopioid medications such as esketamine. Esketamine infusion can relieve postoperative pain in a dose-dependent manner within 24 h, and a higher dose of esketamine can prolong analgesic time and increase sleep quality[16].

A meta-analysis[17] showed that a subanaesthetic dose of ketamine (0.1-0.5 mg/kg) can decrease pain intensity and opioid consumption within 48 h after spinal surgery, but it may cause adverse central nervous system (CNS) events such as hallucination, confusion, disorientation, nightmares, and drowsiness, which can affect the sleep experience. The incidence of CNS adverse events was 13.7%[17]. Qiu et al[15] reported that intraoperative infusion of eskatamine (0.3 mg/kg/h) has a prophylactic effect on PSD in surgical patients, and 1 patient reported having nightmares. Therefore, we will still pay particular attention to the side effects of esketamine, especially CNS adverse events.

Both objective and subjective measures can assess sleep quality. However, it is

worth noting that self-reported perceived sleep can differ from objective findings, including those from actigraphy and polysomnography (PSG), in normal sleepers and insomnia patients[18,19]. Therefore, a comprehensive assessment of sleep often requires a combination of subjective and objective measures. Previous studies on the prophylactic effects of esketamine on PSD in surgical patients lacked objective sleep indicators[15]. Although PSG is the gold standard for objective sleep monitoring, it is impractical for use in the clinical environment, especially for patients after spinal surgery. Alternative devices, such as actigraphy devices, can assess general sleep quality and have been validated in several populations[20]. Therefore, we chose to use a smart wristwatch (Huawei Watch GT3pro, Huawei Technologies Co., Ltd., Shenzhen, China) to monitor objective sleep. Both self-reported subjective measures, including the AIS/PSQI, and objective measures, including total sleep time, light sleep time, deep sleep time and the number of awakenings, will be used for outcomes in our study.

Our study also has several limitations. First, intravenous, nasal spray or oral administration of esketamine alone or in combination has been reported to improve sleep disturbance in depressive patients[21], but our study will only administer esketamine intravenously, and the efficacy and safety of esketamine nasal spray or oral administration for PSD in spinal surgery should be explored in the future. Second, we focused only on the effects of esketamine on perioperative sleep disturbance and did not explore its long-term effects on sleep. Third, our study is a single-center trial, and multicenter trials are needed in the future to verify the effects of esketamine infusion on PSD after other major surgeries.

In summary, this was a double-blinded randomized controlled trial focusing on the effect of esketamine on the subjective and objective sleep quality of patients undergoing spinal surgery. The expected result is that esketamine could improve PSD in these patients without obvious adverse effects.

Ethics approval and consent to participate

The trial was approved by the Ethics Committee of Beijing Tiantan Hospital of

Capital Medical University (KY2024-013-02). Written informed consent will be obtained from all participants.

Consent for publication

Written informed consent for publication will be obtained from all participants.

Availability of data and materials

All data generated or analysed during this study will be included in this published article.

Competing interests

The authors have no potential conflicts of interest to declare with respect to the research, authorship, and/or publication of this article.

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Author contributions

HW and MJ conceived the primary idea of the study. All authors contributed to the writing of the protocol. HW and YC drafted this paper in close cooperation with MJ. The study will be executed by HW, YC, SW, YZ, HL, FL, HQ and MJ. Data analysis will be performed by YC and MJ. All authors have read and approved the final manuscript.

References

1. Halle IH, Westgaard TK, Wahba A, Oksholm T, Rustoen T, Gjeilo KH. Trajectory of sleep disturbances in patients undergoing lung cancer surgery: a prospective study. *Interact Cardiovasc Thorac Surg*. Aug 1 2017;25(2):285-291. doi:10.1093/icvts/ivx076
2. Hillman DR. Sleep Loss in the Hospitalized Patient and Its Influence on Recovery From Illness and Operation. *Anesth Analg*. May 1 2021;132(5):1314-1320. doi:10.1213/ANE.0000000000005323
3. Du J, Zhang H, Ding Z, et al. Development and validation of a nomogram for postoperative sleep disturbance in adults: a prospective survey of 640 patients undergoing spinal surgery. *BMC Anesthesiol*. May 4 2023;23(1):154. doi:10.1186/s12871-023-02097-x
4. Luo M, Song B, Zhu J. Sleep Disturbances After General Anesthesia: Current Perspectives. *Front Neurol*. 2020;11:629. doi:10.3389/fneur.2020.00629
5. Varallo G, Giusti EM, Manna C, et al. Sleep disturbances and sleep disorders as risk factors for chronic postsurgical pain: A systematic review and meta-analysis. *Sleep Med Rev*. Jun 2022;63:101630. doi:10.1016/j.smrv.2022.101630
6. Su X, Wang DX. Improve postoperative sleep: what can we do? *Curr Opin Anaesthesiol*. Feb 2018;31(1):83-88. doi:10.1097/aco.0000000000000538
7. Hu RF, Jiang XY, Chen J, et al. Non-pharmacological interventions for sleep promotion in the intensive care unit. *Cochrane Database Syst Rev*. Oct 6 2015;2015(10):Cd008808. doi:10.1002/14651858.CD008808.pub2
8. Gao Y, Chen X, Zhou Q, et al. Effects of Melatonin Treatment on Perioperative Sleep Quality: A Systematic Review and Meta-Analysis with Trial Sequential Analysis of Randomized Controlled Trials. *Nat Sci Sleep*. 2022;14:1721-1736. doi:10.2147/nss.S381918
9. Cutrufello NJ, Ianus VD, Rowley JA. Opioids and sleep. *Curr Opin Pulm Med*. Nov 2020;26(6):634-641. doi:10.1097/mcp.0000000000000733
10. Wang X, Lin C, Lan L, Liu J. Perioperative intravenous S-ketamine for acute postoperative pain in adults: A systematic review and meta-analysis. *J Clin Anesth*. Feb 2021;68:110071. doi:10.1016/j.jclinane.2020.110071
11. Singh JB, Fedgchin M, Daly E, et al. Intravenous Esketamine in Adult Treatment-Resistant Depression: A Double-Blind, Double-Randomization, Placebo-Controlled Study. *Biol Psychiatry*. Sep 15 2016;80(6):424-431. doi:10.1016/j.biopsych.2015.10.018
12. Song B, Zhu J. A Novel Application of Ketamine for Improving Perioperative Sleep Disturbances. *Nat Sci Sleep*. 2021;13:2251-2266. doi:10.2147/nss.S341161
13. Kohtala S, Alitalo O, Rosenholm M, Rozov S, Rantamäki T. Time is of the essence: Coupling sleep-wake and circadian neurobiology to the antidepressant effects of ketamine. *Pharmacol Ther*. May 2021;221:107741. doi:10.1016/j.pharmthera.2020.107741
14. Duncan WC, Jr., Slonena E, Hejazi NS, et al. Motor-Activity Markers of Circadian Timekeeping Are Related to Ketamine's Rapid Antidepressant Properties. *Biol Psychiatry*. Sep 1 2017;82(5):361-369. doi:10.1016/j.biopsych.2017.03.011

15. Qiu D, Wang XM, Yang JJ, et al. Effect of Intraoperative Esketamine Infusion on Postoperative Sleep Disturbance After Gynecological Laparoscopy: A Randomized Clinical Trial. *JAMA Netw Open*. Dec 1 2022;5(12):e2244514. doi:10.1001/jamanetworkopen.2022.44514
16. Zhu M, Xu S, Ju X, Wang S, Yu X. Effects of the Different Doses of Esketamine on Postoperative Quality of Recovery in Patients Undergoing Modified Radical Mastectomy: A Randomized, Double-Blind, Controlled Trial. *Drug Des Devel Ther*. 2022;16:4291-4299. doi:10.2147/DDDT.S392784
17. Zhou L, Yang H, Hai Y, Cheng Y. Perioperative Low-Dose Ketamine for Postoperative Pain Management in Spine Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Pain Res Manag*. 2022;2022:1507097. doi:10.1155/2022/1507097
18. Bilterys T, Van Looveren E, Malfliet A, et al. Relationship, differences, and agreement between objective and subjective sleep measures in chronic spinal pain patients with comorbid insomnia: a cross-sectional study. *Pain*. Sep 1 2023;164(9):2016-2028. doi:10.1097/j.pain.0000000000002901
19. Allen SF, Elder GJ, Longstaff LF, et al. Exploration of potential objective and subjective daily indicators of sleep health in normal sleepers. *Nat Sci Sleep*. 2018;10:303-312. doi:10.2147/NSS.S168841
20. Van de Water AT, Holmes A, Hurley DA. Objective measurements of sleep for non-laboratory settings as alternatives to polysomnography--a systematic review. *J Sleep Res*. Mar 2011;20(1 Pt 2):183-200. doi:10.1111/j.1365-2869.2009.00814.x
21. Borentain S, Williamson D, Turkoz I, et al. Effect of Sleep Disturbance on Efficacy of Esketamine in Treatment-Resistant Depression: Findings from Randomized Controlled Trials. *Neuropsychiatr Dis Treat*. 2021;17:3459-3470. doi:10.2147/NDT.S339090

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Abstract

Introduction： Postoperative sleep disturbance (PSD) is a common complication after spinal surgery that can be related to postsurgical pain, perioperative anxiety and depression. Recent studies have shown that esketamine may improve sleep disturbance after surgery; however, it remains unclear whether intraoperative infusion of esketamine can improve the postoperative sleep quality of patients undergoing spinal surgery.

Methods and Analysis： This is a protocol for a randomized, double-blinded, placebo-controlled clinical trial to evaluate the effect of esketamine on PSD in patients undergoing spinal surgery. Patients aged 18 to 65 years who plan to undergo selective spinal surgery will be randomly allocated to the esketamine group or control group at a ratio of 1:1. Esketamine or saline will be infused at the same speed of 0.3 mg/kg/h during the surgery by the anaesthesiologists in charge who are blinded to the randomization. The primary outcome of the study is the incidence of postoperative sleep disturbance (PSD) during the first 3 days after surgery. The secondary outcomes include objective sleep quality, NRS scores, dosage of analgesics and Hospital Anxiety and Depression Scale (HADS) scores.

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Keywords: Esketamine, Postoperative sleep disturbance, Spinal surgery

Strengths and limitations of this study

- This study is a randomized controlled trial to evaluate the effect and safety of esketamine on PSD of patients undergoing spinal surgery.
- Participants and evaluators will be blinded to the type of drug administered until the final statistical analyses are completed.
- This study will use both self-reported sleep information and objective sleep information measured by smart wristwatch to measure the sleep quality.
- This study does not include the efficacy and safety of esketamine nasal spray or oral administration for PSD.

Introduction

Postoperative sleep disturbance (PSD), which can result in sleep fragmentation, deprivation, and a reduction in slow-wave sleep (SWS) and rapid eye movement (REM) sleep, is one of the most common complications after major surgery, and its incidence varies from 30-80%[1]. The incidence of PSD after spinal surgery is approximately 61.4%.[2] Previous investigations have reported that continued PSD can cause chronic pain or increased pain sensitivity, heightened stress levels, delirium, gastrointestinal dysfunction, increased risk of cardiovascular events and decreased immune responses[3]. Therefore, sleep promotion is one of the most important ways to help surgical patients recover by reducing delirium, pain, fatigue, and cognitive dysfunction.

PSD is associated with factors such as the type of anaesthesia, postoperative pain, the ward environment, and psychological factors such as preoperative anxiety or depression[6]. Currently, clinical treatments considered to improve PSD include enhanced analgesia and nonpharmacological [7] and pharmacological interventions[8] (such as melatonin). Inadequate pain control, which remains a main problem for postoperative management, can impact patients' sleep and rehabilitation to a large extent[4]. Opioids are commonly used for postoperative analgesia after spinal surgery; however, they do not improve but rather worsen postoperative sleep by decreasing the duration of rapid eye movement (REM) sleep and nonrapid eye movement (NREM) stage 3 sleep and increasing the apnea-hypopnea index (AHI)[9]. Therefore, it is necessary to consider other analgesics and administer multimodal analgesia.

Ketamine, an N-methyl-D-aspartate receptor antagonist, is the only intravenous anaesthetic drug that has both sedative and analgesic effects. Esketamine is a right-handed monomer of ketamine that retains all the advantages of ketamine and has a stronger affinity for NMDA receptors. A meta-analysis[10] showed that esketamine can assist in analgesia and decrease the intensity of pain within 24 h after surgery, as well as reduce the total dosage of opioid analgesics. In addition, previous studies reported that subanaesthetic doses (0.2 and 0.4 mg/kg, intravenously) of esketamine have a rapid and powerful therapeutic effect on

patients with treatment-resistant depression[11]. Recently, there has been increasing interest in its ability to improve sleep disturbance because of its anti-inflammatory, powerful analgesic and antidepressant effects[12]. In addition, esketamine may affect circadian genes to regulate sleep-wake and circadian systems[13]. Duncan et al. reported that ketamine may act on clock-related molecules and brain-derived neurotrophic factor (BDNF) levels, leading to alterations in the circadian rhythm of the central clock; increasing total sleep, rapid eye movement (REM) sleep, and slow-wave sleep; and improving sleep quality in patients with treatment-resistant depression[14]. Initial studies have shown that intraoperative and postoperative infusion of esketamine can improve PSD[15] in patients after gynaecological laparoscopy. However, only a few high-quality clinical studies have confirmed the effect of esketamine on PSD in surgical patients.

Since research on the effect of esketamine on PSD in patients undergoing major spinal surgery is scarce and objective measures of sleep are lacking[15], we will conduct this randomized, double-blinded, placebo-controlled clinical trial. The primary outcome is the incidence of PSD, defined as an Athens Insomnia Scale (AIS) score of 6 points or higher during the first 3 days after surgery. We will also perform objective monitoring of postoperative sleep as a secondary outcome.

Methods/design

Study design

This study is a prospective, single-center, randomized, double-blinded, placebo-controlled clinical trial that will be carried out at Beijing Tiantan Hospital, Capital Medical University. The trial was approved by the Institutional Review Board of Beijing Tiantan Hospital (KY2024-013-02) and registered at ClinicalTrials.gov (NCT 06451627) on June 4,2024. All participants or their legal representatives will sign informed consent (see online supplemental material) after screening and before randomization.

The study is recruiting participants. It started at June 10th, 2024, and the anticipated completion date will be on December 28th, 2025.

Participant recruitment

Inclusion criteria

1. Aged 18 to 65 years.
2. American Society of Anesthesiologist Physical Status classification of I to III.
3. Patients scheduled to undergo elective spinal surgery under general anaesthesia.
4. Signed informed consent.

Exclusion criteria

1. Body mass index (BMI) ≥35 kg/m^2.
2. Severe lesions of important organs.
3. The estimated duration of surgery is more than 4 hours
3. Patients who were retained tracheal intubation or admitted to the intensive care unit (ICU) postoperatively.
4. History of adverse reactions or contraindications to ketamine or esketamine.
5. Cognitive dysfunction, communication disorders.
6. Patients who refused to participate in this study.

Randomization and blinding

All patients scheduled for spinal surgery will be screened 2 days before surgery for eligibility. They will be informed about the aims, procedures, benefits, possible risks of study and how to react if risks occur. Written informed consent will be

obtained during preoperative evaluation by an anesthesiologist. Subsequently, each patient will be randomly allocated to either the esketamine group or the control group at a 1:1 ratio using a variable block randomization method. All study-related investigators will be blinded to the randomization results.

Dispensing and labelling of the study drugs will be performed by an independent nurse. Esketamine (Hengrui Induction, Jiangsu, China) will be diluted to a concentration of 1 mg/mL with normal saline. Both esketamine and normal saline will be kept in syringes (50 mL) with the same appearance and labelled with 'the trial drugs, randomization code'. The trial drug will be given to the participants at a speed of 0.3 mL/kg/h during the surgery. The labelled syringes will be distributed to the attending anesthesiologists responsible for anaesthetic management after induction. The anaesthesiologists, accessors and patients will be blinded to the type of drug administered until the final statistical analyses are completed. The administered drug will be unmasked during medical treatment when severe adverse events related to esketamine occur, with the agreement of the primary investigator.

Anaesthesia management

The baseline characteristics will be collected before anaesthesia including date of birth, gender, height, weight, allergy history, medical history, diagnosis, type of surgery, preoperative sleep quality by Pittsburgh Sleep Quality Index (PSQI) and ASA physical status.

Standard ASA parameters, including blood pressure, electrocardiogram, pulse oxygen saturation, body temperature, and end-tidal carbon dioxide partial pressure ($ETCO_2$), will be monitored perioperatively. Anaesthesia induction will be conducted with 1-2 mg/kg propofol or 0.3 mg/kg etomidate, 0.2-0.4 μg/kg sufentanil and 0.6 mg/kg rocuronium or 0.1-0.15 mg/kg cisatracurium. Total intravenous anaesthesia with propofol, remifentanil and the 'trial drug' will be implemented for anaesthesia maintenance based on the bispectral index (BIS) and maintained between 40 and 60. The surgeon will perform wound infiltration with 20 mL of 0.5% ropivacaine after the last suture.

Patient-controlled analgesia (PCA) devices will be applied after surgery by using

sufentanil (2 μg/kg) and ondansetron (16 mg) in a total volume of 100 ml to maintain NRS scores equal to or less than 3. The device is programmed to administer a background dose of 2 mL/hour, as well as a bolus dose of 0.5 mL with a lockout interval of 15 min for 48 hours. Other analgesics could be used for rescue therapy for severe pain (numerical rating scale score greater than 3) during the postoperative period and should be recorded.

Outcomes

The primary outcome of the study is the incidence of PSD during the first 3 days after surgery, which will be evaluated by the Athens Insomnia Scale (AIS) on the morning (8-10 am) of postoperative days 1-3, and a score of 6 or higher is defined as PSD.

The secondary outcomes included the following:

1. Objective sleeping quality will be assessed with a wristwatch (Huawei Watch GT3pro, Huawei Technologies Co., Ltd., Shenzhen, China) on the first and third nights after surgery. The wristwatch connects to a mobile app via Bluetooth and generates a sleep report that covers total sleep time, light sleep time, deep sleep time, the number of awakenings and so on.

2. Postoperative pain assessment: Postoperative pain at rest and during movement will be evaluated on the morning (8-10 am) of postoperative days 1-3 using an 11-point NRS (0 indicating no pain, 10 indicating the worst pain imaginable). The analgesic consumption and supplemental analgesic use within 72 h will also be recorded.

3. Postoperative anxiety and depression assessment: Postoperative anxiety and depression scores will be measured by the Hospital Anxiety and Depression Scale. On the morning (8-10 am) of postoperative days (PODs) 1 and 3, a score of 8 points or higher indicated depression or anxiety.

Safety outcomes will include all drug-related adverse events, including bradycardia, hypotension, tachycardia, hypertension, arrhythmia, nystagmus, hypersalivation, euphoria, emergence agitation, hallucinations, dreaminess and nightmares during surgery or before discharge. Patients will be followed up for 3

consecutive days (at 8-10 am).

Data management

All paper versions of the original materials, including the protocol, case report forms, and informed consent forms, will be photographed and saved in an encrypted database. All electronic data will be stored in the electronic medical records of Beijing Tiantan Hospital. All procedures for evaluating endpoints will be filmed and saved**.**

Sample size calculation

The PASS 15 software (NCSS, LLC, USA) was used to calculate the sample size based on the primary endpoint. According to the previous study[15], the incidence of PSD after surgery is approximately 44%, and we hypothesized that the incidence of PSD will decrease to 22% after esketamine infusion. Taking this into account, the sample size in each group should be seventy-eight to achieve a power of 80% at a two-tailed significance level of 0.05, with a drop-out rate of 10%.

Statistical analysis

The statistical analysis will be performed by an independent statistician using SPSS 25.0 (Somers, NY, USA). The data will be analysed on a per protocol basis. Descriptive statistics of all variables describing the characteristics of the patients enrolled in the study and those excluded from the study will be analysed. All measurement data will be analysed for a normal distribution and homogeneity of variance. Normally distributed data will be presented as the means ± SDs. Nonnormally distributed data will be presented as medians. Categorical variables will be summarized as percentages and numbers of patients.

The primary endpoint of the incidence of PSD during the first 3 days will be analysed using the $\chi 2$ test or Fisher's exact test. The secondary outcomes will be analysed using t tests, Mann–Whitney U tests and $\chi 2$ or Fisher's exact tests, as appropriate. A logistic regression model will be used to assess the potential risk factors associated with PSD. A two-sided *P* value of less than 0.05 will be considered to indicate statistical significance. No interim analysis will be performed, and the study will be terminated after enrolment of the last patient.

Reporting of adverse events

All adverse events associated with this trial will be recorded in detail and closely monitored until resolution or stabilization or until it has been shown that study treatment is not the cause of the event. The principal investigator will be responsible for reporting all adverse events. Once adverse events occur, they should be immediately reported to the ethics committee within 24 hours and informed to the principal investigator to determine the severity of the adverse events.

Patient and Public Involvement

Patients and the public will not be involved in the trial design. Participants will have access to the findings of the study on request.

Ethics and dissemination

Approval for the study was provided by the Ethical Committee of Beijing Tiantan Hospital, Capital Medical University (KY2024-013-02). The study was registered on clincaltrials.gov on June 4, 2024. The findings of the study will be published in peer-reviewed journals and will be presented at national or international conferences.

Discussion

This study explored the efficacy and safety of intraoperative esketamine infusion on PSD in patients undergoing elective spinal surgery with general anaesthesia. Participants will receive either esketamine or saline infusion at a speed of 0.3 mg/kg/h during the surgery. Moreover, propofol and remifentanil were implemented for anaesthesia maintenance based on the BIS, and the BIS was maintained between 40 and 60. Both subjective and objective sleep measures will be assessed after surgery. The adverse events will also be observed and reported.

Pain is a main cause of PSD in surgical patients and can prolong sleep latency and reduce total sleep time[4]. However, it is extremely difficult to manage postoperative pain in patients undergoing orthopedic surgery, especially spinal surgery. Opioids, commonly used clinical analgesics, have many adverse effects, including respiratory depression, nausea, vomiting, and postoperative hyperalgesia, and can also cause PSD characterized by a reduced duration of slow-wave sleep, rapid eye movement (REM) suppression, and increased duration of arousal [20]. Therefore, multimodal analgesia can better control postoperative pain through nerve blockade and the use of nonopioid medications such as esketamine. Esketamine infusion can relieve postoperative pain in a dose-dependent manner within 24 h, and a higher dose of esketamine can prolong analgesic time and increase sleep quality[16].

A meta-analysis[17] showed that a subanaesthetic dose of ketamine (0.1-0.5 mg/kg) can decrease pain intensity and opioid consumption within 48 h after spinal surgery, but it may cause adverse central nervous system (CNS) events such as hallucination, confusion, disorientation, nightmares, and drowsiness, which can affect the sleep experience. The incidence of CNS adverse events was 13.7%[17]. Qiu et al[15] reported that intraoperative infusion of eskatamine (0.3 mg/kg/h) has a prophylactic effect on PSD in surgical patients, and 1 patient reported having nightmares. Therefore, we will still pay particular attention to the side effects of esketamine, especially CNS adverse events.

Both objective and subjective measures can assess sleep quality. However, it is

worth noting that self-reported perceived sleep can differ from objective findings, including those from actigraphy and polysomnography (PSG), in normal sleepers and insomnia patients[18,19]. Therefore, a comprehensive assessment of sleep often requires a combination of subjective and objective measures. Previous studies on the prophylactic effects of esketamine on PSD in surgical patients lacked objective sleep indicators [15]. Although PSG is the gold standard for objective sleep monitoring, it is impractical for use in the clinical environment, especially for patients after spinal surgery. Alternative devices, such as actigraphy devices, can assess general sleep quality and have been validated in several populations[20]. Therefore, we chose to use a smart wristwatch (Huawei Watch GT3pro, Huawei Technologies Co., Ltd., Shenzhen, China) to monitor objective sleep. Both self-reported subjective measures, including the AIS/PSQI, and objective measures, including total sleep time, light sleep time, deep sleep time and the number of awakenings, will be used for outcomes in our study.

Our study also has several limitations. First, intravenous, nasal spray or oral administration of esketamine alone or in combination has been reported to improve sleep disturbance in depressive patients[21], but our study will only administer esketamine intravenously, and the efficacy and safety of esketamine nasal spray or oral administration for PSD in spinal surgery should be explored in the future. Second, we focused only on the effects of esketamine on perioperative sleep disturbance and did not explore its long-term effects on sleep. Third, our study is a single-center trial, and multicenter trials are needed in the future to verify the effects of esketamine infusion on PSD after other major surgeries. Supplement use of esketamine and dexmedetomidine in patient-controlled sufentanil analgesia have been shown to improve the analgesia and subjective sleep quality after scoliosis correction surgery[22]. Further studies should be performed to investigate whether the postoperative use of esketamine will improve the sleep quality of these patients.

In summary, this is a double-blinded randomized controlled trial focusing on the effect of esketamine on the subjective and objective sleep quality of patients undergoing spinal surgery.

Ethics approval and consent to participate

The trial was approved by the Ethics Committee of Beijing Tiantan Hospital of Capital Medical University (KY2024-013-02). Written informed consent will be obtained from all participants.

Consent for publication

None.

Availability of data and materials

All data generated or analysed during this study will be included in published article. The data that support the findings of this study are available from the corresponding author, HW upon reasonable request.

Competing interests

The authors have no potential conflicts of interest to declare with respect to the research, authorship, and/or publication of this article.

Funding

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Author contributions

HW and MJ conceived the primary idea of the study. All authors contributed to the writing of the protocol. HW and YC drafted this paper in close cooperation with MJ. The study will be executed by HW, YC, SW, YZ, HL, FL, HQ and MJ. Data analysis will be performed by YC and MJ. All authors have read and approved the final manuscript. Huiwen Wang/ HW is responsible for the overall content as guarantor.

References

1. Halle IH, Westgaard TK, Wahba A, Oksholm T, Rustoen T, Gjeilo KH. Trajectory of sleep disturbances in patients undergoing lung cancer surgery: a prospective study. *Interact Cardiovasc Thorac Surg*. Aug 1 2017;25(2):285-291. doi:10.1093/icvts/ivx076
2. Hillman DR. Sleep Loss in the Hospitalized Patient and Its Influence on Recovery From Illness and Operation. *Anesth Analg*. May 1 2021;132(5):1314-1320. doi:10.1213/ANE.0000000000005323
3. Du J, Zhang H, Ding Z, et al. Development and validation of a nomogram for postoperative sleep disturbance in adults: a prospective survey of 640 patients undergoing spinal surgery. *BMC Anesthesiol*. May 4 2023;23(1):154. doi:10.1186/s12871-023-02097-x
4. Luo M, Song B, Zhu J. Sleep Disturbances After General Anesthesia: Current Perspectives. *Front Neurol*. 2020;11:629. doi:10.3389/fneur.2020.00629
5. Varallo G, Giusti EM, Manna C, et al. Sleep disturbances and sleep disorders as risk factors for chronic postsurgical pain: A systematic review and meta-analysis. *Sleep Med Rev*. Jun 2022;63:101630. doi:10.1016/j.smrv.2022.101630
6. Su X, Wang DX. Improve postoperative sleep: what can we do? *Curr Opin Anaesthesiol*. Feb 2018;31(1):83-88. doi:10.1097/aco.0000000000000538
7. Hu RF, Jiang XY, Chen J, et al. Non-pharmacological interventions for sleep promotion in the intensive care unit. *Cochrane Database Syst Rev*. Oct 6 2015;2015(10):Cd008808. doi:10.1002/14651858.CD008808.pub2
8. Gao Y, Chen X, Zhou Q, et al. Effects of Melatonin Treatment on Perioperative Sleep Quality: A Systematic Review and Meta-Analysis with Trial Sequential Analysis of Randomized Controlled Trials. *Nat Sci Sleep*. 2022;14:1721-1736. doi:10.2147/nss.S381918
9. Cutrufello NJ, Ianus VD, Rowley JA. Opioids and sleep. *Curr Opin Pulm Med*. Nov 2020;26(6):634-641. doi:10.1097/mcp.0000000000000733
10. Wang X, Lin C, Lan L, Liu J. Perioperative intravenous S-ketamine for acute postoperative pain in adults: A systematic review and meta-analysis. *J Clin Anesth*. Feb 2021;68:110071. doi:10.1016/j.jclinane.2020.110071
11. Singh JB, Fedgchin M, Daly E, et al. Intravenous Esketamine in Adult Treatment-Resistant Depression: A Double-Blind, Double-Randomization, Placebo-Controlled Study. *Biol Psychiatry*. Sep 15 2016;80(6):424-431. doi:10.1016/j.biopsych.2015.10.018
12. Song B, Zhu J. A Novel Application of Ketamine for Improving Perioperative Sleep Disturbances. *Nat Sci Sleep*. 2021;13:2251-2266. doi:10.2147/nss.S341161
13. Kohtala S, Alitalo O, Rosenholm M, Rozov S, Rantamäki T. Time is of the essence: Coupling sleep-wake and circadian neurobiology to the antidepressant effects of ketamine. *Pharmacol Ther*. May 2021;221:107741. doi:10.1016/j.pharmthera.2020.107741
14. Duncan WC, Jr., Slonena E, Hejazi NS, et al. Motor-Activity Markers of Circadian Timekeeping Are Related to Ketamine's Rapid Antidepressant Properties. *Biol Psychiatry*. Sep 1 2017;82(5):361-369. doi:10.1016/j.biopsych.2017.03.011

15. Qiu D, Wang XM, Yang JJ, et al. Effect of Intraoperative Esketamine Infusion on Postoperative Sleep Disturbance After Gynecological Laparoscopy: A Randomized Clinical Trial. *JAMA Netw Open*. Dec 1 2022;5(12):e2244514. doi:10.1001/jamanetworkopen.2022.44514
16. Zhu M, Xu S, Ju X, Wang S, Yu X. Effects of the Different Doses of Esketamine on Postoperative Quality of Recovery in Patients Undergoing Modified Radical Mastectomy: A Randomized, Double-Blind, Controlled Trial. *Drug Des Devel Ther*. 2022;16:4291-4299. doi:10.2147/DDDT.S392784
17. Zhou L, Yang H, Hai Y, Cheng Y. Perioperative Low-Dose Ketamine for Postoperative Pain Management in Spine Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Pain Res Manag*. 2022;2022:1507097. doi:10.1155/2022/1507097
18. Bilterys T, Van Looveren E, Malfliet A, et al. Relationship, differences, and agreement between objective and subjective sleep measures in chronic spinal pain patients with comorbid insomnia: a cross-sectional study. *Pain*. Sep 1 2023;164(9):2016-2028. doi:10.1097/j.pain.0000000000002901
19. Allen SF, Elder GJ, Longstaff LF, et al. Exploration of potential objective and subjective daily indicators of sleep health in normal sleepers. *Nat Sci Sleep*. 2018;10:303-312. doi:10.2147/NSS.S168841
20. Van de Water AT, Holmes A, Hurley DA. Objective measurements of sleep for non-laboratory settings as alternatives to polysomnography--a systematic review. *J Sleep Res*. Mar 2011;20(1 Pt 2):183-200. doi:10.1111/j.1365-2869.2009.00814.x
21. Borentain S, Williamson D, Turkoz I, et al. Effect of Sleep Disturbance on Efficacy of Esketamine in Treatment-Resistant Depression: Findings from Randomized Controlled Trials. *Neuropsychiatr Dis Treat*. 2021;17:3459-3470. doi:10.2147/NDT.S339090

INFORMED CONSENT

Effect of esketamine on postoperative sleep disturbance in patients undergoing spinal surgery: a randomized, double-blinded, placebo-controlled clinical trial

Project entrust organization: Beijing Tiantan Hospital

Contract Research Organization: N/A

Version： 2.0

2nd, January, 2024

INFORMATION SHEET

You will receive ***spinal surgery***. We would like to invite you to participate our study, which is ***" Effect of esketamine on postoperative sleep disturbance in patients undergoing spinal surgery: a randomized, double-blinded, placebo-controlled clinical trial"***, to evaluate the effect of esketamine on the PSD of patients undergoing spinal surgery. This study is approved by Ethics Committee of Beijing Tiantan Hospital of Capital Medical University. During our study, we will follow the Declaration of Helsinki.

Before you decide whether participate this clinical trial, please take time to review this information carefully. This form describes the purpose, procedure, study duration, risks, and possible benefits of participating the study. You may also wish to talk to others, including your friends, family, or discuss with your anesthesiologist about your participation in this study.

1. PURPOSE of THIS STUDY

Postoperative sleep disturbance (PSD), which can result in sleep fragmentation, deprivation, and a reduction in slow-wave sleep (SWS) and rapid eye movement (REM) sleep, is one of the most common complications after major surgery, and its incidence varies from 30-80%. The incidence of PSD after spinal surgery is approximately 61.4%. Previous investigations have reported that continued PSD can cause chronic pain or increased pain sensitivity, heightened stress levels, delirium, gastrointestinal dysfunction, increased risk of cardiovascular events and decreased immune responses. Therefore, sleep promotion is one of the most important ways to help surgical patients recover by reducing delirium, pain, fatigue, and cognitive dysfunction.

Esketamine is a right-handed monomer of ketamine that retains all the advantages of ketamine and has a stronger affinity for NMDA receptors. Recently, there has been increasing interest in its ability to improve sleep disturbance because of its anti-inflammatory, powerful analgesic and antidepressant effects. Since research on the effect of esketamine on PSD in patients undergoing major spinal surgery is scarce and objective measures of sleep are lacking, we conducted this randomized, double-blinded, placebo-controlled clinical trial.

2. NUMBER of PARTICIPANTS

In total, 156 patients will be included in the study.

3. WHO WILL PARTICIPANT IN THIS STUDY

- Age range from 18 to 65 years old
- American Society of Anaesthesiologists (ASA) physical status I to III
- The patient underwent elective spinal surgery under general anaesthesia.

4. WHO SHOULD NOT PARTICIPATE in the STUDY

If you have following condition, you should not participate in the study:

- Body mass index (BMI) $\geqslant$35 kg/m^2.
- Severe lesions of important organs.
- The patient underwent tracheal intubation or was admitted to the intensive care unit (ICU) postoperatively.

- History of adverse reactions or contraindications to ketamine or esketamine.
- Cognitive dysfunction, communication disorders.
- Patients who refused to participate in this study.

5. DURATION OF THIS STURY

This study will only be conducted during your hospital stay. You will be followed up at 24h, 48h, 72h after surgery for any adverse reactions, and your sleep quality will be assessed.

You can opt out of the research at any time without losing any benefits you should have received. However, if you decide to withdraw from this study during the study, we encourage you to consult with your doctor first. Considering your security issues, there may be a related check after you log out.

6. PROCESS OF THIS STUDY

If you are willing to participate in this study, your doctor will learn about your medical history, ask about your current disease, and current treatment medications to further confirm whether you are suitable for participating in this study.

If you are willing to participate in this study, during the general anesthesia of the operation, you have a half chance of using esketamine. There is also a one-half possibility of using saline. The incidence of post operative sleep disturbance will be assessed.

The day before your scheduled surgery, the researcher will determine whether you meet the inclusion-exclusion criteria of this study based on your disease and current status. If you agree to participate in the research, we will interview your medical details. After 24h, 48h, 72h, the researcher will examine your condition again. All visits will not cause you any harm. Participation in this study does not require changes to your surgical methods and postoperative treatment. Except for randomly entering a study group and receiving different administration methods of muscle relaxants, other anaesthesia management will not be affected in any way. Both medication regimens are safe. If you enter any research group, we will try your best to ensure that your surgery goes smoothly.

7. POSSIBLE BENEFITS of PARTICIPATING in the STUDY

The depth of anaesthesia will be under our strict monitoring during the operation. The results obtained from this study may perioperative anaesthesia management plans and improve PSD in patients undergoing spinal surgery.

8. POSSIBLE ADVERSE REACTIONS, RISKS and DISCOMFORT, INCONVENIENCES of PARTICIPATING in the STUDY

The adverse reactions of esketamine include bradycardia, hypotension, tachycardia, hypertension, arrhythmia, nystagmus, hypersalivation, euphoria, emergence agitation, hallucinations, dreaminess and nightmares. In this study, the dosage of esketamine is small and will not cause obvious adverse reactions. We have also formulated a detailed response plan if any adverse reactions occur after surgery; hypertension and tachycardia can be relieved by giving antihypertensive drugs.

If your health does suffer from research-related damage due to participation in this research, please notify the doctor immediately, who will be responsible for taking appropriate treatment

measures for you. The sponsor, Beijing Tiatan Hospital, will bear the cost of treatment and provide you with corresponding financial compensation in accordance with relevant national regulations.Even if you have signed this informed consent form, you still retain all your legal rights.

9. OTHER TREATMENT CHOICE

If you do not participate in this study, you can choose your anesthesia treatment according to your anesthesiologist's suggestion.

10. YOU MAY VOLUNTARILY CHOOSE TO PARTICIPATE in the STUDY and WITHDRAW from the STUDY

Whether to participate in the study is entirely up to you. You may refuse to participate in the study or withdraw from the study at any time during the study, which will not affect your relationship with your doctor or affect your medical service or other benefits.

Before making decision, you can discuss with your family or friend， or you can talk with your doctor for any question, until you fully understand this study.

11. RELATED EXPENSES

Anesthetic drugs and surgical procedures are not free of charge. If you combine the treatment and examination required for other diseases, and if the treatment fails, the cost of changing to other treatment is not free of charge. If any medical expense happened due to adverse event, you will be exempted from the charge.

12. CONFIDENTIALITY of PERSONAL INFORMATION

Your medical records (study records /CRF, lab sheets, etc.) will be kept intact at the hospital. Your doctor will record the results of tests and other tests on your medical record. Researchers, ethics committees, and drug regulators will be allowed access to your medical records. Any public reports on the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical data within the law.

13. HOW TO GET MORE INFORMATION?

You can ask any questions about this study at any time and get answers. Your anesthesiologist will be ready to answer any of your questions before, during and after the study.

14. HOW THE STUDY MAY EFFECT YOUR LIFE?

You may feel the visit and examination uncomfortable and special arrangement is needed. You can consult your doctor in any steps of the study.

15. CONSULTING

If you have any related questions, please contact Dr. Jian Minyu (phone: 010-59976656 or cell phone: 13522550438).

If you have any concerns about your personal benefits, or you want to complain or express your concerns about the study, please contact the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (phone：010-59975178, email: ttyyirb@163.com)

SINGATURE PAGE OF AGREEMENT

Study title: Effect of esketamine on postoperative sleep disturbance in patients undergoing spinal surgery: a randomized, double-blinded, placebo-controlled clinical trial

Principal Investigator: Ruquan Han, Beijing Tiantan Hospital, CMU

DECLARATION of CONSENT

I have read the introduction about the study above and have the opportunity to discuss with doctors and ask the questions about the study. All my questions have been answered satisfactorily.

I am aware of the possible risk and benefits of participating in this study. I know that participating in the study is voluntary. I have taken it into full consideration, and known that:

- I can ask my doctor for more information at any time.
- I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

I am also aware that if I withdraw from the study, especially if I withdraw due to medication, it will be of great benefit to the whole study if I tell my doctor about my condition and complete the corresponding physical examination and physical and chemical inspection.

If I need to take any other medication due to a change in my condition, I will consult my doctor beforehand or tell him afterwards truthfully.

I agree that the ethics committee of the drug regulatory authority or the representative of the sponsor may have access to my research information.

I will be provided with a signed and dated copy of the informed consent.

In the end, I agreed to participate in the study and promised to follow my doctors' advice as much as possible.

Signature of patient/legal relative:_____

Relation: _____

Date: _____ **(yyyy/mm/dd)**

I confirm that I have explained the details of the trial to the patients, including its rights and possible benefits and risks, and have given them a signed copy of the informed consent.

Signature of doctor:_____

Date: _____ **(yyyy/mm/dd)**