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Opioid-free anaesthesia and postoperative quality of recovery of supratentorial tumour neurosurgery: Protocol for a randomized, controlled trial

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Opioid-free anaesthesia and postoperative quality of recovery of supratentorial tumour neurosurgery: Protocol for a randomized, controlled trial

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Competing interests statement: The authors have no conflicts of interest to disclose.

Abstract

Background Opioids play a pivotal role in neurosurgical anaesthesia and are capable of effectively blocking the pain and stress responses triggered by procedures such as surgery and intubation. However, it should not be overlooked that opioids have numerous side effects, such as respiratory depression, postoperative nausea, and vomiting. Opioid-free anaesthesia can prevent or significantly reduce opioid usage. This study aimed to investigate the efficacy and safety of opioid-free anaesthesia in neurosurgical supratentorial tumor surgeries.

Methods and analysis: This is a single-center, prospective, randomized, controlled clinical trial. A total of 170 patients receiving general anaesthesia were randomized at a 1:1 ratio into two groups, one receiving opioid-free anaesthesia and the other receiving opioid-based anaesthesia. The primary outcome measure was the quality of recovery-15 score on the second day after surgery. The other parameters included the quality of recovery score on the 5th day, the incidence of nausea and vomiting within 48 hours, the NRS pain score on the second and 5th days, etc.

Ethics and dissemination: Following a rigorous review process, this study received official approval from the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University on September 9, 2024 (KY2024-219-02) and was registered on Clinicaltrials.gov on September 15, 2024 (NCT06607029). The inclusion date for the first patient was October 21, 2024. This randomized controlled trial investigated the feasibility of opioid-free anaesthesia for neurosurgery. The findings of this study are intended to be disseminated through publications in international peer-reviewed journals, presentations at national and international academic conferences, and broad distribution via online platforms.

Trial registration number: Clinicaltrials.gov NCT06607029, September 15, 2024

Keywords: Esketamine, Multimodal analgesia, Opioid-free anaesthesia, Quality of recovery

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Strengths and limitations of this study

- This study is a prospective randomized controlled study to explore the safety and efficacy of opioid-free anaesthesia in neurosurgery patients, with a high level of evidence and reference value.
- In this study, the QOR-15 score was used to evaluate various aspects of patients’ postoperative recovery, such as comfort, pain and emotion.
- In terms of pain assessment, this study focused not only on perioperative acute pain but also on chronic pain 3 months after surgery.
- This study included patients who underwent supratentorial tumor resection during neurosurgery, and the effectiveness of opioid-free anaesthesia for patients with intracranial aneurysms, nasal endoscopic surgery, and skull base tumor resection remains unclear.

INTRODUCTION

Opioids play a pivotal role in neurosurgical anaesthesia and are capable of effectively blocking the pain and stress responses triggered by procedures such as surgery and intubation^{1 2}. However, it should not be overlooked that opioids have numerous side effects, such as respiratory depression, postoperative nausea, and vomiting. These side effects not only prolong the patient's hospital stay but also further increase medical costs^{2 3}. In addition, opioid use disorder is becoming a global public health crisis. Nearly 50,000 people in the United States die each year from opioid-related causes, and another 480,000 people could die from opioid overdoses in the next 10 years⁴. Perioperative opioid overdose is believed to be a significant factor in this crisis⁴. It is necessary to find a low- or opioid-free anaesthesia strategy that reduces or avoids the use of opioids while achieving the same good perioperative analgesic effects as opioids.

Opioid-free anaesthesia is a multimodal anaesthesia strategy that combines a variety of nonopioid drugs or techniques that act on different nociceptive pathways. Neurosurgery is characterized by changes in pain intensity during the operation. The period of head nail fixation and cranial opening and closing is a period of intense pain stimulation, whereas the period of tumor resection is a period of low pain stimulation⁵. Scalp nerve block can effectively block painful intraoperative irritation while producing the additional benefit of postoperative analgesia, reducing the dose of general anaesthetics used⁶. Therefore, scalp nerve blocks can be used to prevent painful stimulation and avoid the use of opioids. Furthermore, perfect oropharyngeal surface anaesthesia can be blocked by tracheal intubation to a certain extent.

At present, opioid-free anaesthesia has not been widely used in neurosurgical clinical practice. Few studies have indicated that, compared with opioid anaesthesia, scalp nerve block in combination with the use of dexmedetomidine and acetaminophen opioid-free anaesthesia does not have any disadvantages in terms of the average pain score at 0--12 hours or 0--24 hours after surgery [9]. However, there are certain limitations in this study, such as a relatively low level of evidence and a limited sample size.

This randomized controlled study explored the impact of an opioid-free anaesthesia protocol on the recovery quality of patients after supratentorial tumor resection and further

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comprehensively explored the feasibility of this anaesthesia method in a group of neurosurgical patients.

METHODS AND ANALYSIS

Trial setting and eligibility criteria

This trial is a single-center, randomized, controlled, patient and outcome assessor-blinded trial conducted at Beijing Tiantan Hospital, Capital Medical University. A study coordinator screens elective neurosurgery patients daily to determine eligibility. The inclusion criteria were as follows: scheduled to undergo craniotomy for supratentorial tumors with general anaesthesia; 18 years≤age≤65 years; American Society of Anesthesiologists (ASA) physical status of I to III; and signed informed consent (Supplement 1). The exclusion criteria were as follows: patients with a body mass index (BMI)≥35 kg/m²; patients with severe hepatic and renal insufficiency; patients with cognitive dysfunction, aphasia or other states that did not cooperate with the assessment; patients with preoperative magnetic resonance imaging of the head showing midline displacement >5 mm⁷; patients who underwent electrophysiological monitoring during surgery; and pregnant or lactating patients. If severe bleeding or serious adverse events occurred during the operation, the study was terminated. The schedules of the activities for the registration, intervention, and assessment of the participants are shown in Table 1 and Figure 1.

Discontinuation or withdrawal of study subjects

Each participant has the right to withdraw from the research at any time for any reason voluntarily, and the researcher may also stop a subject's involvement for any number of reasons, most commonly protocol infractions or safety concerns.

Assignment of interventions

Patients identified as eligible by the study investigator will be randomly assigned to the opioid-free anaesthesia group or the opioid-based control group at a 1:1 ratio. Randomization will take place on the day of surgery. The table of random numbers will be generated by independent

researchers via computer software. In this study, block randomization was adopted, and the block length was 4. The random codes were sealed opaque envelopes. Before anaesthesia begins, the envelopes will be opened by researchers who are unaware of the randomization procedure, and the subjects will be assigned to either the opioid-free anaesthesia group or the opioid-based control group. Because of the specificity of the intervention method, the anesthesiologist knew the grouping of patients, but the surgeon and other members of the medical team did not. The participants and primary outcome evaluators will be blinded. The randomization results will be known only when patients experienced a serious adverse event (such as death or life-threatening emergency rescue) that required additional visits.

Interventions

Patients in the opioid-free anaesthesia group were given 0.5 µg/kg dexmedetomidine infusion within 5–10 min before the induction of anaesthesia. Anaesthesia will be induced with 1–1.5 mg/kg lidocaine, 5 µg/ml propofol, and 0.6–0.8 mg/kg rocuronium after loss of consciousness. A visual laryngoscope will be placed to expose the epiglottis and glottis, and oral pharyngeal surface anaesthesia will be administered with 2% lidocaine. The needles were sprayed evenly in the airway, vocal cords and epiglottic laryngeal surface. Mask ventilation was continued after surface anaesthesia, and endotracheal intubation was performed after the effects of lidocaine and propofol on the chamber concentration reached 2.5 µg/ml. After induction of anaesthesia, bilateral scalp nerve block will be performed with 0.5% ropivacaine. The scalp nerve blocks included the supraorbital nerve, supratrochlear nerve, auriculotemporal nerve, zygomaticotemporal nerve, major occipital nerve and minor occipital nerve. The nerve block site was selected according to the location of the surgical incision and head nail, and 2–3 ml of local anaesthetic was injected into each block site. Anaesthesia will be maintained with a 0.5 minimum alveolar concentration (MAC) of sevoflurane or desflurane combined with 0.12 mg/kg/h esketamine, 0.4 µg/kg/h dexmedetomidine, and 2.0–2.5 µg/ml propofol TCI.

For patients in the opioid-based control group, 0.3–0.5 µg/kg sufentanil, 5 µg/ml propofol, and 0.6–0.8 mg/kg rocuronium will be used for anaesthesia induction. Anaesthesia will be maintained with a 0.5 minimum alveolar concentration (MAC) of sevoflurane or desflurane

combined with 0.05–0.2 µg/kg/min of remifentanyl and 2.0–2.5 µg/ml propofol TCI. Sufentanil will be administered intermittently at 0.1 µg/kg as required by surgery.

Standardized anaesthesia management

Standardized anaesthesia management will be adopted for all patients. The intravenous route will be established according to anaesthesia and surgical requirements after admission. Electrocardiograms, heart rate, blood pressure and pulse oxygen saturation will be routinely monitored. Rocuronium bromide will be added intermittently according to the course of surgery. The respiratory parameters should be regulated, the patient should be properly hyperventilated, and blood PaCO₂ should be maintained at 30–35 mmHg. The BIS values of 40--60 will be maintained. After the operation, the sevoflurane was removed, and the fresh gas flow was adjusted to 6 L/min. All the subjects were given 8 mg of ondansetron intravenously during anaesthesia to prevent postoperative nausea and vomiting. For subjects with severe nausea and vomiting (three or more episodes of vomiting or inability to perform daily activities due to nausea and vomiting), additional medications such as ondansetron may be administered for postoperative remedial antiemetic therapy. Patients with postoperative pain scores ≥4 can be given analgesic drugs, such as oxycodone and acetaminophen, for postoperative remedial analgesic treatment, and all drugs should be recorded in detail (Supplement 2).

Primary outcome

The primary outcome measure was the quality of recovery-15 (QoR-15) score on the second day after surgery. The QoR-15 scale is used to evaluate the postoperative recovery of patients in five dimensions: pain, physical comfort, physical independence, psychological support and emotional state⁸. Each item is scored on a 10-point scale ranging from 0 (worst recovery) to 150 (best recovery)⁸. According to the results of previous meta-analyses, a change in the QoR-15 scale score to 6 points is considered to be clinically significant⁹⁻¹¹.

Secondary outcomes

The secondary outcomes in this study included the QoR-15 score on the 5th day after surgery;

the incidence of nausea and vomiting within 48 hours after surgery (including nausea, retching, or vomiting episodes); the NRS pain score on the second and 5th days after surgery; the sleep quality on the second and 5th days after surgery; and the incidence of chronic pain at 3 and 6 months after surgery. Perioperative sleep quality will be assessed via the Athens Insomnia Scale (AIS).

Data collection

At patient enrollment, the researchers will collect the demographic and baseline characteristics of the patients. Patients' vital signs, anaesthetic administration, fluid volume, blood loss, and urine volume were recorded intraoperatively. The quality of recovery, pain score, sleep quality, postoperative nausea and vomiting, postoperative complications and adverse events will be recorded during postoperative follow-up. Pain scores will be obtained by telephone at 3 and 6 months after surgery. Follow-up is still needed for patients who withdraw or change their treatment regimen.

Data management

Raw data for all patients will be collected via paper case report forms specially designed by the researchers and placed in dedicated lockers with locks. The paper case report form for this study will be destroyed three years after the end of the study. The electronic data of this study will be stored encrypted after hiding personal information. Only leading researchers have access to the electronic database. All researchers involved in this study will strictly abide by the rules of professional confidentiality and keep all personal information of patients confidential.

Sample size

According to previous data from our center, the QoR-15 score of neurosurgery patients on the second day after surgery was 109±14. Changes of up to 6 points on the QoR-15 scale are considered clinically significant⁹⁻¹¹. The test efficacy is 80%, the bilateral α is 0.05, and the required sample size is 162 cases according to the PASS statistical software. Considering the 5% shedding rate, this study planned to recruit 170 subjects.

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Statistical methods

This study adopted the principle of intention-to-treat analysis; all analyses were conducted by researchers who were unaware of the intervention, and primary outcomes were analysed via per-protocol analysis. The continuous variables designed in this study will be tested for normality via the Kolmogorov–Smirnov test. Data conforming to a normal distribution will be expressed as the mean ± standard deviation, and nonnormally distributed data will be expressed as the median and interquartile range. The t test will be used for continuous variables that conform to a normal distribution, and the Mann–Whitney U test will be used for continuous variables that do not conform to a normal distribution. Categorical variables are expressed as percentages and were analysed via chi-square tests, corrected chi-square tests, or Fisher’s exact tests. Intraoperative hemodynamic parameters, including systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate, will be compared between the two groups via repetitive measurement deviation analysis. A P value of 0.05 or less (double-tailed letter level) was considered statistically significant.

Data safety and monitoring

The accuracy and security of all the data are governed by an appointed data monitoring committee. The data monitoring board is independent of the researchers and includes an anesthesiologist, a neurosurgeon, and a biostatistician. The data monitoring committee will review the contents of the database every six months to ensure that all the data are collected accurately and in a timely manner.

Serious adverse events

An adverse event was defined as an adverse event or worsening of a preexisting medical condition that occurred during the study period, whether or not it was related to the intervention in this study. All adverse events associated with this study will be closely monitored until the adverse events are resolved and the condition stabilizes. Researchers are required to closely monitor and record adverse events and report adverse events to the ethics committee within 24

hours of their occurrence.

ETHICS AND DISSEMINATION

Research ethics approval and consent process

This study was performed in accordance with the principles of the Declaration of Helsinki. Prior to the study, the study was approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (KY2024-219-02) (Supplement 3). The investigator will present the study to the patient or his/her legal representative the day before the procedure, and the patient or his/her legal representative will sign a written informed consent form on the day of the procedure. This protocol was prepared in accordance with the requirements of the SPIRIT 2013 guidelines.

Protocol amendments

The principal investigator has the right to modify the study protocol. The principal investigator will need to communicate with the research department before implementing the revised protocol. Changes to the study protocol will be subject to approval by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University.

Confidentiality and access to data

The randomization results of this study will be stored in an opaque envelope that is coded and identified according to the order in which patients are enrolled. All the subjects' paper copies will be stored in a locked cabinet. The electronic data of the subject are stored encrypted after the personal information is concealed. Only the principal investigator has access to the final database.

Dissemination policy

No patient or member of the public will be involved in the design, recruitment or clinical implementation of this study. The findings will be disseminated to all study participants at the end of the study.

Declaration interests

All participants in this study declare that they do not have any financial or other conflicts of interest.

DISCUSSION

This prospective randomized controlled study investigated the efficacy and safety of an opioid-free anaesthesia regimen in neurosurgical patients. Opioids are a double-edged sword that are effective analgesics but also inevitably cause respiratory depression, nausea and vomiting, hyperalgesia, immune suppression, skin itching, myoclonus and other adverse reactions. These side effects can lead to delayed recovery, longer hospital stays, and increased health care costs²³. Enhanced recovery after surgery (ERAS) recommends reducing perioperative opioid use or adopting an opioid-free anaesthesia regimen to improve the quality of patients' perioperative recovery^{12 13}.

Given the limited effects of surface anaesthesia and nerve blocking, we used a combination of other nonopioid analgesics, such as dexmedetomidine and esketamine, during the perioperative period. Dexmedetomidine is a highly selective α_2 -adrenergic receptor agonist with sedative and analgesic effects¹⁴⁻¹⁶. The analgesic effect of dexmedetomidine is different from that of opioids, and it can inhibit inflammation and oxidative stress through a variety of pathways, producing neuroprotective effects¹⁵. In addition, dexmedetomidine reduces injurious input and delivery by activating α_2 receptors in the dorsal horn of the spinal cord¹⁷. We administered dexamethasone intravenously to patients in the opioid-free anaesthesia group prior to induction to suppress the stress response induced by tracheal intubation. Esketamine is an S-enantiomer of racemic ketamine and has a higher affinity for the N-methyl-D-aspartate receptor than does ketamine¹⁸. Esketamine has excellent analgesic effects and is increasingly used for perioperative pain management¹⁸⁻²¹.

In addition to focusing on the analgesic effects of opioid-free anaesthesia strategies in neurosurgical patients, this study focused on the quality of perioperative recovery. The primary outcome measure was the quality of recovery-15 (QoR-15) score on the second day after

surgery. The QoR-15 scale, a tool used to evaluate recovery quality during the perioperative period, has the advantages of strong effectiveness and a sensitive response⁹. Opioid-free anaesthesia has been widely used in a variety of nonneurosurgical procedures to improve the quality of patients' perioperative recovery. A randomized controlled study of 115 breast cancer patients revealed that nonopioid anaesthesia via thoracic paravertebral nerve block improved the quality of early postoperative recovery without compromising pain control in patients who underwent breast cancer surgery²². Randomized controlled studies of patients undergoing laparoscopic cholecystectomy have shown that the 15-item quality of recovery questionnaire (QoR-15) scores of patients without opioid anaesthesia on the first and second days after surgery are higher than those of patients under opioid anaesthesia²³.

In conclusion, the successful completion of this trial and the validation of its underlying hypotheses will provide evidence for the use of opioid-free anaesthesia in neurosurgery patients. If the results are positive, new perioperative management strategies may be developed for neurosurgical patients.

Trial status

This clinical study is currently in the recruitment phase. The study recruited the first patient on October 21, 2024, and the estimated study completion date will be October 31, 2025.

Author contributions: YF drafted the manuscript for this protocol. YF, YZ, YC, YW, TW, YL and RH initiated the study design and refined the research protocol. YY provided statistical analysis guidance. YF, YZ, YC, YW, TW, YL and YY contributed to data collection and manuscript revision. RH is the grant holder and the corresponding author. All the authors have read and approved the final manuscript.

Patient and public involvement: Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Patients and public involvement

Patients and the public were not directly consulted during the formulation of the research questions or outcome measurements. None of the patients participated in this study's design, recruitment, or clinical implementation. There will be a manuscript to present the trial results after the study. The study's results will also be disseminated to all study participants via their preferred method.

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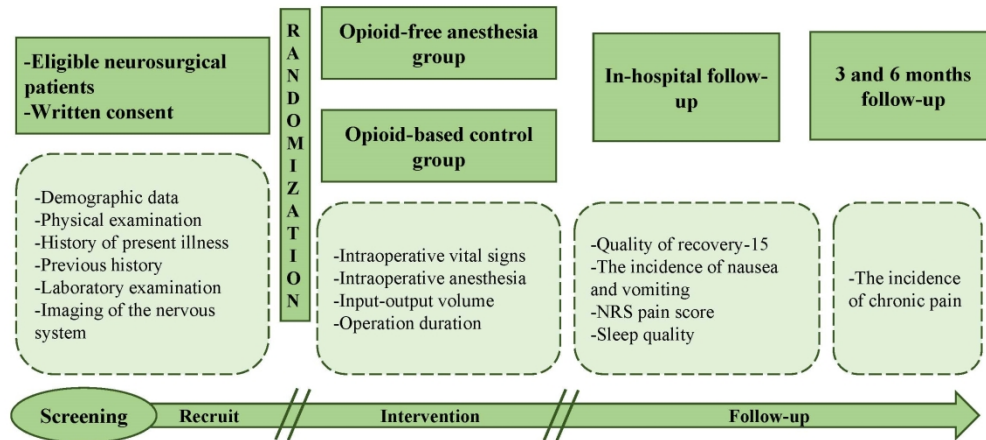
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338x190mm (200 x 200 DPI)

Supplement 2 Standard anaesthetic management

1. The intravenous route will be established according to anaesthesia and surgical requirements after admission. Electrocardiograms, heart rate, blood pressure and pulse oxygen saturation will be routinely monitored.

2. Anaesthetic methods: intravenous and inhaled combined anaesthesia. Rocuronium bromide will be added intermittently according to the course of surgery.

3. Mechanical ventilation is initiated with the following parameters: tidal volume, 6–8 mL/kg; respiratory rate, 12–15/min; inspiratory/expiratory ratio, 1:2; inspired oxygen concentration, 60%; and fresh gas flow, 1–2 L/min. The respiratory parameters should be regulated, the patient should be properly hyperventilated, and blood PaCO₂ should be maintained at 30–35 mmHg. After the operation, the sevoflurane was removed, and the fresh gas flow was adjusted to 6 L/min.

4. Hemodynamic management: The anesthesiologist maintains intraoperative blood pressure within 20% of the patient's baseline blood pressure.

5. The BIS is maintained between 40 and 50.

6. All the subjects were given 8 mg of ondansetron intravenously during anaesthesia to prevent postoperative nausea and vomiting. For subjects with severe nausea and vomiting (three or more episodes of vomiting or inability to perform daily activities due to nausea and vomiting), additional medications such as ondansetron may be administered for postoperative remedial antiemetic therapy.

7. Patients with postoperative pain scores ≥ 4 can be given analgesic drugs, such as oxycodone and acetaminophen, for postoperative remedial analgesic treatment.

伦理审查批件AF/02-06, 01/08, 0

首都医科大学附属北京天坛医院医学伦理委员会
IRB of Beijing Tiantan Hospital, Capital Medical University

伦理审查批件
Approval Letter

| | |
|---------------|--|
| 伦理审查编号 | KY2024-219-02 |
| 项目全称 (编号) | 无阿片类药物麻醉对神经外科幕上肿瘤切除术患者围术期恢复质量的影响：一项随机对照研究 |
| 申办者/CRO | 首都医科大学附属北京天坛医院 |
| 研究类别 | <div><input type="checkbox"/> 药物临床试验</div> <div><input type="checkbox"/> 医疗器械临床试验</div> <div><input checked="" type="checkbox"/> 科研立项</div> |
| 主要研究者/科室 | 韩如泉/麻醉科 |
| 审查日期 | 2024/09/09 |
| 审查地点 | 首都医科大学附属北京天坛医院 |
| 伦理委员会 评审文件 | <div>1. 初次伦理审查申请</div> <div>2. 立项证明材料</div> <div>3. 本中心主要研究者简历、执业证书、职称证书、GCP 培训证书</div> <div>4. 研究团队成员名单</div> <div>5. 研究团队利益冲突声明</div> <div>6. 研究材料诚信承诺书</div> <div>7. 临床研究方案 (版本号: 2.0 版本日期: 2024-08-28)</div> <div>8. 研究项目方案相关材料</div> <div>9. 论文开题报告考核评分表</div> <div>10. 知情同意书 (版本号: 2.0 版本日期: 2024-08-28)</div> <div>11. 病例报告表样表 (版本号: 1.0 版本日期: 2024-05-22)</div> <div>12. 研究者手册 (版本号: 1.0 版本日期: 2024-05-22)</div> <div>13. 复审申请表</div> <div>14. 修改说明表</div> |
| 伦理审查方式 | <div><input type="checkbox"/> 会议审查</div> <div><input checked="" type="checkbox"/> 快速审查</div> |
| 审查意见 | |

根据我国新颁发的《涉及人的生命科学和医学研究伦理审查办法》、《涉及人的生物医学研究伦理审查办法》、《医疗技术临床应用管理办法》、《药物临床试验伦理审查工作指导原则》、《药物临床试验质量管理规范》、《医疗器械临床试验质量管理规范》，以及新颁发的 ICH-GCP、世界医学会《赫尔辛基宣言》、WHO 和国际医学科学组织委员会《涉及人的健康相关研究国际伦理准则》的伦理原则等，经本伦理委员会审查：

同意 按临床研究方案进行 **无阿片类药物麻醉对神经外科幕上肿瘤切除术患者围术期恢复质量的影响：一项随机对照研究** 临床研究。

备注：无

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|-------------------------|---|------|---------------|
| 年度/定期跟踪审查日期 | 请于 2025 年 09 月 08 日前 1 个月提交年度/定期跟踪审查（跟踪频率：12 个月） | | |
| 批件有效期 | 1 年 | 联系电话 | 59978555/5692 |
| 主任委员签字 |  | 批准日期 | 2024/09/09 |
| 首都医科大学附属北京天坛医院伦理委员会（盖章） | | | |

- 声明：
1. 批件有效期：本试验应在批准后 1 年内实施，逾期未实施本批件自行废止。
 2. 北京天坛医院伦理委员会的职责、人员组成、操作规程和记录遵循我国 NMPA 颁布的 GCP 和 ICH GCP 的伦理审查原则，并遵守我国相关法律法规的规定。
 3. “同意”的研究应遵循本伦理委员会批准的方案执行，应符合 GCP 和赫尔辛基宣言的原则。
 4. “不同意”和“暂停或终止”的研究方案，申办者和研究者可就审查意见和建议中提及的问题做书面申诉，并陈述理由。本伦理委员会可就申诉作重新审查。
 5. 被暂停的研究，若想重新开始，在暂停之日起 6 个月内向伦理委员会提交申请（复审申请），伦理委员会批准后方可开始。超过 6 个月不再受理。
 6. 研究过程中，对研究方案、知情同意书、招募材料所作的任何修改，或更换主要研究者，均需递交“修改方案审查申请”，伦理委员会审查同意后后方可实施。
 7. 研究中发生的安全性事件，研究者应根据 GCP 要求，及时报告本伦理委员会审查。
 8. 本中心发生的严重违背方案或持续违背方案，应及时报告本伦理委员会审查。
 9. 年度/定期研究进展报告：请研究者/申办者根据跟踪审查日期与频率，在规定日期前 1 个月递交跟踪审查报告。
 10. 研究结束时，请向伦理委员会递交结题报告和分中心小结表。
 11. 各类申请报告与疑问，请登录网址：www.bjtht.org/Home/，→医学伦理委员会

IRB of Beijing Tiantan Hospital, Capital Medical University

IRB review suggestions

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|-----------------------------------|---|
| Ethics review No | KY2024-219-02 |
| Title of the project | Opioid-free anaesthesia and postoperative quality of recovery of supratentorial tumour neurosurgery: a randomized controlled trial |
| Sponsor/CRO | Beijing Tiantan Hospital, Capital Medical University |
| Principal investigator/Department | Ruquan Han/ Department of Anesthesiology |
| Review date | September 9, 2024 |
| Review location | Beijing Tiantan Hospital, Capital Medical University |
| Review documents | 1. Application for initial ethical review 2. Project certification materials 3. Resume of the main researcher of the center, practicing certificate, title certificate, GCP training certificate 4. Research team members list 5. Research team conflict of interest statement 6. Research the material integrity pledge 7. Clinical research protocol (V2.0; 2024-08-28) 8. Research project program-related materials 9. Paper proposal report assessment score table |

| | | | |
|---|---|----------------|--------------------|
| | 10. Informed consent (V2.0; 2024-08-28) 11. Sample case report form (V1.0; 2024-05-22) 12. Researcher Handbook (V1.0; 2024-05-22) 13. Application for review 14. Modify the description table | | |
| Ethical review method | <input type="checkbox"/> Meeting review <input checked="" type="checkbox"/> Rapid review | | |
| Review comments | <p>According to China's newly promulgated Measures for the Ethical Review of Life Science and Medical Research Involving Humans, Measures for the Ethical Review of Biomedical Research Involving Humans, Measures for the Administration of Clinical Application of Medical Technology, Guiding Principles for the Ethical Review of Drug Clinical Trials, Good Practice for the Quality Control of Drug Clinical Trials, and Good Practice for the Quality Control of Medical Device Clinical Trials, As well as the ethical principles of the newly promulgated ICH-CGP, the Declaration of Helsinki of the World Medical Association, the International Ethical Guidelines for Health-related Research Involving Human Beings of WHO and the Committee of International Organizations of Medical Sciences, etc., after review by this Ethics Committee, it is agreed to conduct this clinical study in accordance with the clinical research protocol.</p> <p>Note: None.</p> <p>Please submit annual/periodic follow-up review one month before September 8, 2025 (follow-up frequency: 12 months)</p> | | |
| Signature of chairperson | | Contact number | 59978555/5692 |
| IRB of Beijing Tiantan Hospital, Capital Medical University | | Date | September 09, 2024 |
| | | | |

Table 1 Schedule of enrollment, interventions, data collection and outcome assessments

| Time point | Operation | | Postoperation follow-up | | | |
|---|-------------------|-------------------|-------------------------|------------------------|---------|---------|
| | Pre- Operation | Dur- Operation | 2d after surgery | 5d after surgery | 3months | 6months |
| Enrollment | | | | | | |
| Eligibility screen | × | | | | | |
| Recruitment | × | | | | | |
| Consent | × | | | | | |
| Randomization and allocation | × | | | | | |
| Intervention | | | | | | |
| Opioid-free anaesthesia group or opioid-based control group | | × | | | | |
| Prerandomization data collection | | | | | | |
| Demographics | × | | | | | |
| Physical examination | × | | | | | |
| Laboratory results | × | | | | | |
| Neurological examination | × | | | | | |
| Daily data collection | | | | | | |
| Intraoperative vital signs | | × | | | | |
| The use of antiemetic drugs | | | × | | | |
| The use of analgesic drugs | | | × | × | × | × |
| Laboratory results | | | × | × | | |
| Primary outcome | | | | | | |

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| QoR-15 score on the second day after surgery | | | × | | | |
| Secondary outcomes | | | | | | |
| QoR-15 score on the 5th day after surgery | | | | × | | |
| Postoperative nausea and vomiting | | | × | | | |
| NRS pain score | | | × | × | × | × |
| Postoperative sleep quality | | | × | × | | |

QoR, quality of recovery; NRS, numerical rating scale

BMJ Open

Opioid-free anaesthesia and postoperative quality of recovery of supratentorial tumour neurosurgery: Protocol for a randomised, controlled trial

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|---------------------------------|--|
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| Article Type: | Protocol |
| Date Submitted by the Author: | 24-Mar-2025 |
| Complete List of Authors: | Fu, Yuxuan; Beijing Tiantan Hospital, Department of Anesthesiology, Beijing Tiantan Hospital, Capital Medical University Zhou, Yang; Beijing Tiantan Hospital, Department of Anesthesiology, Beijing Tiantan Hospital, Capital Medical University Cui, Yidan; Beijing Nuclear Industry Hospital Wu, Youxuan; Beijing Tiantan Hospital, Department of Anesthesiology, Beijing Tiantan Hospital, Capital Medical University Wang, Tianyuan; Beijing Tiantan Hospital, Department of Anesthesiology, Beijing Tiantan Hospital, Capital Medical University Li, Yang; Beijing Tiantan Hospital, Department of Anesthesiology, Beijing Tiantan Hospital, Capital Medical University Yu, Yun; Beijing Tiantan Hospital, Department of Anesthesiology, Beijing Tiantan Hospital, Capital Medical University Han, Ruquan; Beijing Tiantan Hospital, Department of Anesthesiology, Beijing Tiantan Hospital, Capital Medical University |
| Primary Subject Heading: | Anaesthesia |
| Secondary Subject Heading: | Anaesthesia |
| Keywords: | Anaesthesia in neurology < ANAESTHETICS, Neurosurgery < SURGERY, Clinical Protocols, Pain management < ANAESTHETICS |
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**Opioid-free anaesthesia and postoperative quality of recovery of supratentorial
tumour neurosurgery: Protocol for a randomised, controlled trial**

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Wang, M.D. *; Yang Li, M.D. *; Yun Yu, M.D. *; Ruquan Han, M.D., PhD *

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Running title: OFA for neurosurgery

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Competing interest statement: The authors have no conflicts of interest to disclose.

Abstract

Background Opioids play a pivotal role in neurosurgical anaesthesia and are capable of effectively blocking the pain and stress responses triggered by procedures such as surgery and intubation. However, it should not be overlooked that opioids have numerous side effects, such as respiratory depression, postoperative nausea, and vomiting. Opioid-free anaesthesia can prevent or significantly reduce opioid usage. The aim of this study was to investigate the effect of opioid-free anaesthesia on the quality of recovery in patients undergoing supratentorial tumour resection in neurosurgery.

Methods and analysis: This is a single-centre, prospective, randomised, controlled clinical trial. A total of 170 patients receiving general anaesthesia are randomised at a 1:1 ratio into two groups, one receiving opioid-free anaesthesia and the other receiving opioid-based anaesthesia. The primary outcome measure was the quality of recovery-15 score on the second day after surgery. The secondary outcomes included the quality of recovery score on the 5th day, the incidence of nausea and vomiting within 48 hours, the NRS pain score on the second and 5th days, the sleep quality on the second and 5th days after surgery, and the incidence of chronic pain at 3 and 6 months after surgery.

Ethics and dissemination: Following a rigorous review process, this study received official approval from the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University, on September 9, 2024 (KY2024-219-02) and was registered on Clinicaltrials.gov on September 15, 2024 (NCT06607029). The inclusion date for the first patient was October 21, 2024. The findings of this study are intended to be disseminated through publications in international peer-reviewed journals, presentations at national and international academic conferences, and broad distribution via online platforms.

Trial registration number: Clinicaltrials.gov NCT06607029, September 15, 2024

Keywords: Esketamine, Multimodal analgesia, Opioid-free anaesthesia, Quality of recovery

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54 **Strengths and limitations of this study**

- 55 ● This study is a prospective randomised controlled study with a high level of evidence.
- 56 ● The QOR-15 score is a multidimensional, comprehensive assessment of patient recovery
- 57 quality and is easy to implement.
- 58 ● In terms of pain assessment, this study focused not only on perioperative acute pain but
- 59 also on chronic pain after surgery.
- 60 ● The researchers who performed the postoperative follow-up were unaware of the group
- 61 assignment.
- 62 ● This study has certain limitations. This study included patients who underwent
- 63 supratentorial tumor resection during neurosurgery, and whether opioid-free anaesthesia
- 64 improves the quality of recovery in patients who underwent intracranial aneurysm and
- 65 endoscopic nasal surgery is unclear.

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INTRODUCTION

Opioids play a pivotal role in neurosurgical anaesthesia and are capable of effectively blocking the pain and stress responses triggered by procedures such as surgery and intubation^{1 2}. However, it should not be overlooked that opioids have numerous side effects, such as respiratory depression, postoperative nausea, and vomiting. The incidence of postoperative nausea and vomiting in neurosurgical patients is as high as 73%, which may lead to increased intracranial pressure, cerebral perfusion and electrolyte imbalance, seriously affecting prognosis^{3 4}. In addition, 2%-6% of patients who had no previous opioid addiction exhibited continued opioid use after surgery⁵. It is necessary to find a low- or opioid-free anaesthesia strategy that reduces or avoids the use of opioids while achieving the same good perioperative analgesic effects as opioids.

Opioid-free anaesthesia is a multimodal anaesthesia strategy that combines a variety of nonopioid drugs or techniques that act on different nociceptive pathways. The main characteristic of neurosurgery is that pain stimulation occurs during the periods of overhead fixation, cranial opening and closing. Scalp nerve block can effectively block pain during this period and play a role in postoperative analgesia^{6 7}. At present, opioid-free anaesthesia has not been widely used in neurosurgical clinical practice. Few studies have indicated that, compared with opioid anaesthesia, scalp nerve block in combination with the use of dexmedetomidine and acetaminophen opioid-free anaesthesia does not have any disadvantages in terms of the average pain score at 0--12 hours or 0--24 hours after surgery⁸. However, there are certain limitations in this study, such as a relatively low level of evidence and a limited sample size.

This study hypothesized that an opioid-free anaesthesia protocol could improve the quality of perioperative recovery in patients undergoing neurosurgical supratentorial tumour resection.

METHODS AND ANALYSIS

Trial setting and eligibility criteria

This trial is a single-centre, randomised, controlled, patient and outcome assessor-blinded trial conducted at Beijing Tiantan Hospital, Capital Medical University. A study coordinator screens elective neurosurgery patients daily to determine eligibility. The inclusion criteria were as follows: scheduled to undergo craniotomy for supratentorial tumours with general anaesthesia; 18 years≤age≤65 years; American Society of Anaesthesiologists (ASA) physical status of I to

III; and signed informed consent (Supplement 1). The exclusion criteria were as follows: body mass index (BMI)≥35 kg/m²; severe hepatic or renal insufficiency; cognitive dysfunction, aphasia or other states that did not cooperate with the assessment; preoperative magnetic resonance imaging of the head showing midline displacement >5 mm⁹; electrophysiological monitoring during surgery; and pregnancy or lactation. The schedules of the activities for the registration, intervention, and assessment of the participants are shown in Table 1 and Figure 1.

Table 1 Schedule of enrollment, interventions, data collection and outcome assessments

| Time point | Operation | | Postoperation follow-up | | | |
|---|---------------|---------------|-------------------------|------------------|---------|---------|
| | Pre-Operation | Dur-Operation | 2d after surgery | 5d after surgery | 3months | 6months |
| Enrollment | | | | | | |
| Eligibility screen | × | | | | | |
| Recruitment | × | | | | | |
| Consent | × | | | | | |
| Randomization and allocation | × | | | | | |
| Intervention | | | | | | |
| Opioid-free anaesthesia group or opioid-based control group | | × | | | | |
| Prerandomization data collection | | | | | | |
| Demographics | × | | | | | |
| Physical examination | × | | | | | |
| Laboratory results | × | | | | | |
| Neurological examination | × | | | | | |
| Daily data collection | | | | | | |
| Intraoperative vital signs | | × | | | | |

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|--|--|--|---|---|---|---|
| The use of antiemetic drugs | | | × | | | |
| The use of analgesic drugs | | | × | × | × | × |
| Laboratory results | | | × | × | | |
| Primary outcome | | | | | | |
| QoR-15 score on the second day after surgery | | | × | | | |
| Secondary outcomes | | | | | | |
| QoR-15 score on the 5th day after surgery | | | | × | | |
| Postoperative nausea and vomiting | | | × | | | |
| NRS pain score | | | × | × | × | × |
| Postoperative sleep quality | | | × | × | | |

QoR, quality of recovery; NRS, numerical rating scale

Discontinuation or withdrawal of study subjects

Each participant has the right to withdraw from the research at any time for any reason voluntarily, and the researcher may also stop a subject's involvement for any number of reasons, most commonly protocol infractions or safety concerns.

Assignment of interventions

Patients identified as eligible by the study investigator will be randomly assigned to the opioid-free anaesthesia group or the opioid-based control group at a 1:1 ratio. Randomisation was performed on the day of surgery. The table of random numbers was generated by independent researchers via computer software (SPSS 26.0). In this study, block randomization is adopted, and the block length is 4. The subjects' random results are placed in light-tight envelopes

numbered in strict accordance with their enrollment order. The researchers open the envelopes in the order in which they are assigned, ensuring that the assignment information is unpredictable. Before anaesthesia begins, the envelopes are opened by researchers who are unaware of the randomization procedure, and the subjects are assigned to either the opioid-free anaesthesia group or the opioid-based control group. Because of the specificity of the intervention method, the anaesthesiologist knew the grouping of patients, but the surgeon and other members of the medical team did not. The participants and primary outcome evaluators were blinded. The randomisation results are known only when patients experienced a serious adverse event (such as death or life-threatening emergency rescue) that required additional visits.

Interventions

Patients in the opioid-free anaesthesia group were not given opioids during the procedure. Anaesthesia is induced with 1–1.5 mg/kg lidocaine, 1.5–2.5 mg/kg propofol or 0.15–0.3 mg/kg etomidate, and 0.6–0.8 mg/kg rocuronium after loss of consciousness. A visual laryngoscope was placed to expose the epiglottis and glottis, and oral pharyngeal surface anaesthesia was administered with 2% lidocaine. The needles are sprayed evenly in the airway, vocal cords and epiglottic laryngeal surface. Mask ventilation was continued after surface anaesthesia, and endotracheal intubation was performed after lidocaine surface anaesthesia took effect. After induction of anaesthesia, bilateral scalp nerve block was performed with 0.5% ropivacaine. The scalp nerve blocks included the supraorbital nerve, supratrochlear nerve, auriculotemporal nerve, zygomaticotemporal nerve, major occipital nerve and minor occipital nerve. The nerve block site is selected according to the location of the surgical incision and head nail, and 2–3 ml of local anaesthetic is injected into each block site. Scalp nerve blocks are performed by an anaesthesiologist under ultrasound guidance. Dexamethasone is not used as a local anaesthetic for nerve block. Anaesthesia is maintained with a 0.3–0.6 minimum alveolar concentration (MAC) of sevoflurane or desflurane combined with 0.12 mg/kg/h esketamine, 0.4–0.6 µg/kg/h dexmedetomidine, and 2–4 mg/kg/h propofol. The anaesthesiologist may adjust the drug type and dosage (without opioids) according to the specific situation of each subject, and all medications must be recorded in detail. If there are any adverse events associated with

esketamine and dexmetopidine during the procedure, such as severe bradycardia, the medication should be discontinued, and opioids may be appropriately administered to ensure a smooth operation. If patients in the opioid-free anaesthesia group have strong pain stimulation during surgery, resulting in persistent tachycardia or elevated blood pressure, opioid analgesia can be appropriately administered to ensure stable haemodynamics.

For patients in the opioid-based control group, 0.3–0.5 µg/kg sufentanil, 1.5–2.5 mg/kg propofol or 0.15–0.3 mg/kg etomidate, and 0.6–0.8 mg/kg rocuronium were used for anaesthesia induction. Anaesthesia was maintained with a 0.3–0.6 minimum alveolar concentration (MAC) of sevoflurane or desflurane combined with 0.05–0.2 µg/kg/min of remifentanyl and 2–4 mg/kg/h propofol. Sufentanil is administered intermittently at 0.1 µg/kg as required by surgery. The anaesthesiologist can adjust the drug type and dosage according to the specific situation of each subject, and all medications should be recorded in detail.

Standardized anaesthesia management

Standardized anaesthesia management was adopted for all patients. The intravenous route is established according to anaesthesia and surgical requirements after admission. Electrocardiograms, heart rate, blood pressure and pulse oxygen saturation are routinely monitored. Rocuronium bromide was added intermittently according to the course of surgery. The respiratory parameters should be regulated, the patient should be properly hyperventilated, and blood PaCO₂ should be maintained at 30–35 mmHg. The anaesthesiologist, on the basis of the patient's response to the drug, adjusts the dose of the sedative drugs (propofol and sevoflurane) to ensure that the BIS is between 40 and 50. After the operation, the sevoflurane was removed, and the fresh gas flow was adjusted to 6 L/min. All the subjects were given 8 mg of ondansetron intravenously during anaesthesia to prevent postoperative nausea and vomiting. For subjects with severe nausea and vomiting (three or more episodes of vomiting or inability to perform daily activities due to nausea and vomiting), additional medications such as ondansetron may be administered for postoperative remedial antiemetic therapy. Patients with postoperative pain scores ≥ 4 can be given analgesic drugs, such as oxycodone and acetaminophen, for postoperative remedial analgesic treatment, and all drugs should be recorded in detail (Supplement 2). If intraoperative blood loss exceeds 40% of the blood volume

or if there are other adverse events that threaten the life of the patient, the study is terminated, and opioids can be given as needed. The anaesthesiologist should actively handle the situation according to the situation and record the processing process.

Primary outcome

The primary outcome measure was the quality of recovery-15 (QoR-15) score on the second day after surgery. The QoR-15 scale is used to evaluate the postoperative recovery of patients in five dimensions: pain, physical comfort, physical independence, psychological support and emotional state¹⁰. Each item is scored on a 10-point scale ranging from 0 (worst recovery) to 150 (best recovery)¹⁰. According to the results of previous meta-analyses, a change in the QoR-15 scale score to 6 points is considered to be clinically significant¹¹⁻¹³.

Secondary outcomes

The secondary outcomes in this study included the QoR-15 score on the 5th day after surgery; the incidence of nausea and vomiting within 48 hours after surgery (including nausea, retching, or vomiting episodes); the NRS (Numerical Rating Scale) pain score on the second and 5th days after surgery; the sleep quality on the second and 5th days after surgery; and the incidence of chronic pain at 3 and 6 months after surgery¹⁴. Chronic pain is defined as pain that lasts longer than 3 months¹⁴. Perioperative sleep quality was assessed via the Athens Insomnia Scale (AIS). Safety indicators, including the incidence of intraoperative bradycardia (heart rate < 60 bpm), tachycardia (heart rate > 100 bpm), hypertension (more than 30% of baseline blood pressure and requiring drug intervention), hypotension (less than 30% of baseline blood pressure and requiring drug intervention) and postoperative intracranial hemorrhage, should also be considered.

Data collection

At patient enrollment, the researchers collected the demographic and baseline characteristics of the patients. Patients' vital signs, anaesthetic administration, fluid volume, blood loss, and urine volume were recorded intraoperatively. The quality of recovery, pain score, sleep quality, postoperative nausea and vomiting, postoperative complications and adverse events were

recorded during postoperative follow-up. Pain scores were obtained via telephone at 3 and 6 months after surgery. The researchers also collected information on the percentage of patients in the opioid-free anaesthesia group who used opioids. Considering the influence of the pathological type of a tumor on patient prognosis, researchers should also collect the pathological results of patients after surgery. All participants enrolled in the randomization were followed up until six months after surgery. To promote the participation of the subjects in this study and ensure the integrity of the data, we collected the contact information of their families in addition to the subjects for follow-up after discharge. All patients in our centre use electronic versions of medical records and anaesthesia sheets. In this study, a paper case report form was used to record the information of the participants.

Data management

Raw data for all patients are collected via paper case report forms specially designed by the researchers and placed in dedicated lockers with locks. The paper case report form for this study was destroyed three years after the end of the study. The electronic data of this study are stored encrypted after hiding personal information. Only leading researchers have access to the electronic database. All researchers involved in this study strictly abided by the rules of professional confidentiality and keep all personal information of patients confidential.

Sample size

According to unpublished data from a preliminary study of 20 patients in our centre, the QoR-15 score of neurosurgery patients on the second day after surgery was 109 ± 14 . Changes of up to 6 points on the QoR-15 scale are considered clinically significant¹¹⁻¹³. Finally, with the use of the PASS-15, a total of 170 patients were needed to detect differences in the primary outcome with 80% power and a two-sided alpha of 0.05, allowing for a 5% loss to follow-up.

Statistical methods

All patients enrolled in the randomisation process, including those who discontinued the study due to intraoperative adverse events such as bleeding, were included in a modified intentionality analysis. The primary outcome will be analysed via modified intentionality analysis and per-

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protocol analysis. All analyses will be conducted by researchers who are unaware of the intervention. The continuous variables used in this study were tested for normality via the Kolmogorov–Smirnov test. Data conforming to a normal distribution will be expressed as the mean \pm standard deviation, and nonnormally distributed data will be expressed as the median and interquartile range. The t test will be used for continuous variables that conform to a normal distribution, and the Mann–Whitney U test will be used for continuous variables that do not conform to a normal distribution. Categorical variables are expressed as percentages and were analysed via chi-square tests, corrected chi-square tests, or Fisher’s exact tests. Intraoperative haemodynamic parameters, including systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate, will be compared between the two groups via repetitive measurement deviation analysis. For the missing data, the last observation and the worst-case imputation scenarios are used as the main interpolation methods. A P value of 0.05 or less (double-tailed letter level) was considered statistically significant. No interim analysis is planned for this study.

Data safety and monitoring

The accuracy and security of all the data are governed by an appointed data monitoring committee. The Data Safety Monitoring Board is independent of the researchers and includes an anaesthesiologist, a neurosurgeon, and a biostatistician. The data monitoring committee will review the contents of the database every six months to ensure that all the data are collected accurately and in a timely manner. The principal investigator regularly monitored and tracked the anaesthesiologist's compliance with the protocol.

Serious adverse events

An adverse event was defined as an adverse event or worsening of a preexisting medical condition that occurred during the study period, whether or not it was related to the intervention in this study. All adverse events associated with this study will be closely monitored until the adverse events are resolved and the condition stabilizes. Adverse events are reported to the research department immediately after they occur, and the severity of the adverse events is determined by the principal investigator. In addition, the principal investigator should report

269 this information to the Ethics Committee (IRB) within 24 hours. The Data Monitoring Board
270 will be responsible for monitoring clinical safety and reviewing all adverse events reported to
271 the IRB to determine the risks and benefits of the study. If a patient's health is compromised as
272 a result of participation in this study, we will be responsible for receiving appropriate treatment.
273 Beijing Tiantan Hospital will pay for the treatment of patients in accordance with relevant
274 national regulations and pay corresponding financial compensation to patients.

275

276 **ETHICS AND DISSEMINATION**

277 **Research ethics approval and consent process**

278 This study was performed in accordance with the principles of the Declaration of Helsinki.
279 Prior to the study, the study was approved by the Ethics Committee of Beijing Tiantan Hospital,
280 Capital Medical University (KY2024-219-02). The investigator will present the study to the
281 patient or his/her legal representative the day before the procedure, and the patient or his/her
282 legal representative will sign a written informed consent form on the day of the procedure. This
283 protocol was prepared in accordance with the requirements of the SPIRIT 2013 guidelines.

284

285 **Protocol amendments**

286 The principal investigator has the right to modify the study protocol. The principal investigator
287 will need to communicate with the research department before implementing the revised
288 protocol. Changes to the study protocol will be subject to approval by the Ethics Committee of
289 Beijing Tiantan Hospital, Capital Medical University.

290

291 **Confidentiality and access to data**

292 The randomisation results of this study will be stored in an opaque envelope that is coded and
293 identified according to the order in which patients are enrolled. All the subjects' paper copies
294 will be stored in a locked cabinet. The electronic data of the subject are stored encrypted after
295 the personal information is concealed. Only the principal investigator has access to the final
296 database.

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298 **Dissemination policy**

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The findings will be disseminated to all study participants at the end of the study. The findings of this study are intended to be disseminated through publications in international peer-reviewed journals, presentations at national and international academic conferences, and broad distribution via online platforms.

Declaration interests

All participants in this study declare that they do not have any financial or other conflicts of interest.

Data Availability Statement

The deidentified participant data reported in this study could be made available to researchers upon approval by the corresponding author (Dr. Ruquan Han, ruquan.han@ccmu.edu.cn) immediately after publication. The reasonable request should provide a formal protocol for database use that has been approved by the ethics institutions.

DISCUSSION

This prospective randomised controlled study investigated whether an opioid-free anaesthesia regimen could improve the quality of perioperative recovery in neurosurgery patients. Opioids are a double-edged sword that are effective analgesics but also inevitably cause respiratory depression, nausea and vomiting, hyperalgesia, immune suppression, skin itching, myoclonus and other adverse reactions. These side effects can lead to delayed recovery, longer hospital stays, and increased health care costs^{2 15}. Enhanced recovery after surgery (ERAS) recommends reducing perioperative opioid use or adopting an opioid-free anaesthesia regimen to improve the quality of patients' perioperative recovery^{16 17}. In addition, opioid use disorder is becoming a global public health crisis. Nearly 50,000 people in the United States die each year from opioid-related causes, and excessive perioperative opioid prescription has been identified as a significant cause¹⁸.

Given the limited effects of surface anaesthesia and nerve blocking, we used a combination of other nonopioid analgesics, such as dexmetopmine and esketamine, during the perioperative

period. Dexmedetomidine is a highly selective α_2 -adrenergic receptor agonist with sedative and analgesic effects¹⁹⁻²¹. The analgesic effect of dexmedetomidine is different from that of opioids, and it can inhibit inflammation and oxidative stress through a variety of pathways, producing neuroprotective effects²⁰. In addition, dexmedetomidine reduces injurious input and delivery by activating α_2 receptors in the dorsal horn of the spinal cord²². We administered dexamethasone intravenously to patients in the opioid-free anaesthesia group prior to induction to suppress the stress response induced by tracheal intubation. Esketamine is an S-enantiomer of racemic ketamine and has a higher affinity for the N-methyl-D-aspartate receptor than does ketamine²³. Esketamine has excellent analgesic effects and is increasingly used for perioperative pain management²³⁻²⁶.

At present, opioid-free anaesthesia is not widely used in neurosurgical clinical practice. A previous study validated the feasibility of opioid-free anaesthesia in neurosurgical patients⁸. The study prospectively enrolled six patients for craniotomy via opioid-free anaesthesia. These six patients were matched to 18 patients who were anaesthetized with opioids by age, sex, incision length, and incision location⁸. Scalp nerve block in combination with the use of dexmedetomidine and acetaminophen opioid-free anaesthesia does not have any disadvantages in terms of the average pain score at 0--12 hours or 0--24 hours after surgery⁸. However, there are certain limitations in this study, such as a relatively low level of evidence and a limited sample size. Our study is a large prospective study with high-quality evidence that can compensate for the limitations of previous studies.

In addition to focusing on the analgesic effects of opioid-free anaesthesia strategies in neurosurgical patients, this study focused on the quality of perioperative recovery. The primary outcome measure was the quality of recovery-15 (QoR-15) score on the second day after surgery. The QoR-15 scale, a tool used to evaluate recovery quality during the perioperative period, has the advantages of strong effectiveness and a sensitive response¹¹. Opioid-free anaesthesia has been widely used in a variety of nonneurosurgical procedures to improve the quality of patients' perioperative recovery. A randomised controlled study of 115 breast cancer patients revealed that nonopioid anaesthesia via thoracic paravertebral nerve block improved the quality of early postoperative recovery without compromising pain control in patients who

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underwent breast cancer surgery²⁷. Randomised controlled studies of patients undergoing laparoscopic cholecystectomy have shown that the 15-item quality of recovery questionnaire (QoR-15) scores of patients without opioid anaesthesia on the first and second days after surgery are higher than those of patients under opioid anaesthesia²⁸.

In conclusion, the successful completion of this trial and the validation of its underlying hypotheses will provide evidence for the use of opioid-free anaesthesia in neurosurgery patients. If the results are positive, new perioperative management strategies may be developed for neurosurgical patients.

Trial status

This clinical study is currently in the recruitment phase. The study recruited the first patient on October 21, 2024, and the estimated study completion date will be October 31, 2025.

Author contributions: YF drafted the manuscript for this protocol. YF, YZ, YC, YW, TW, YL and RH initiated the study design and refined the research protocol. YY provided statistical analysis guidance. YF, YZ, YC, YW, TW, YL and YY contributed to data collection and manuscript revision. RH is the grant holder and the corresponding author. All the authors have read and approved the final manuscript. Ruquan Han is the guarantor.

Patients and public involvement

Patients and the public were not directly consulted during the formulation of the research questions or outcome measurements. None of the patients participated in this study's design, recruitment, or clinical implementation. There will be a manuscript to present the trial results after the study. The study's results will also be disseminated to all study participants via their preferred method.

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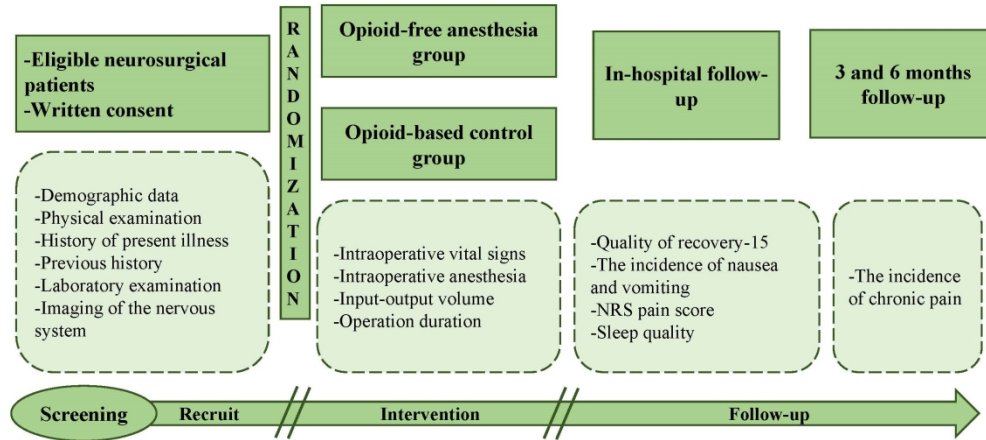
FIGURE LEGENDS

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475 Figure 1 Study implementation flow chart

476 NRS, Numerical Rating Scale

For peer review only



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Informed consent

Name of the research scheme: Opioid-free anaesthesia and
postoperative quality of recovery of supratentorial tumour
neurosurgery: a randomized controlled trial

Applicant: Beijing Tiantan Hospital, Capital Medical University

Dear patient,

We invite you to participate in the study " Opioid-free anaesthesia and postoperative quality of recovery of supratentorial tumour neurosurgery: a randomized controlled trial " approved by Beijing Tiantan Hospital Affiliated to Capital Medical University. The study will be conducted at Beijing Tiantan Hospital affiliated to Capital Medical University, and an estimated 170 participants will voluntarily participate. Participation in this study is voluntary. Some of the content covered in this paper is subject to regulatory requirements and has been reviewed and approved by the Ethics Committee of Beijing Tiantan Hospital affiliated to Capital Medical University in order to protect the rights and interests of the patients participating in the study.

1. Why was this study conducted?

Background: Opioids are the most effective drugs for the treatment of pain, and are an important part of general anesthesia, and are the most widely used anti-nociceptive drugs in the perioperative period. Opioids have many side effects, such as constipation, urinary retention, itchy skin, respiratory depression, and postoperative nausea and vomiting. These side effects can lead to delayed recovery, longer hospital stays, and increased health care costs. In recent years, with the concept of rapid rehabilitation surgery after surgery, a new perioperative analgesia strategy model is called opioid-free anesthesia. Rapid rehabilitation surgery theory emphasizes reducing perioperative opioid use to improve the quality of patients' perioperative recovery.

Purpose: We conducted this randomized controlled study to provide clinical evidence for the efficacy and safety of opioid-free anesthesia in neurosurgical patients.

2. How many people will participate in the study?

About 170 people will participate in the study at Beijing Tiantan Hospital affiliated to Capital Medical University, and 170 people are planned to participate in the study.

3. Who are selected to participate in the study?

Our inclusion criteria included: 18 years≤age≤65 years; American Society of Anesthesiologists (ASA) physical status of I to III; and signed informed consent. Whether or not you can participate in the study needs to be examined by a doctor.

4. Who should not participate in the study?

Our exclusion criteria included: patients with a body mass index (BMI)≥35 kg/m²; patients with severe hepatic and renal insufficiency; patients with cognitive dysfunction, aphasia or other states that did not cooperate with the assessment; patients with preoperative magnetic resonance imaging of the head showing midline displacement >5 mm⁷; patients who underwent electrophysiological monitoring during surgery; and pregnant or lactating patients. If you are in any of the above criteria, you are not included in this study.

5. How long will the study last?

The study will last for 2 years. If you participate in the study, you will need to collect some medical information from the date of enrollment to the time of discharge, and follow up until the fifth day after surgery. You can opt out of the study at any time without forfeiting any benefits you would otherwise have received. However, if during the study you decide to withdraw from the study, we encourage you to consult with your doctor first. In view of your security concerns, it is possible that a relevant check will be conducted after the exit.

6. How was the study conducted?

If you are willing to participate in the study, your doctor will review your medical history, ask about past and current therapeutic medications, and undergo a routine preoperative

examination to further confirm your suitability for participation in the study. By randomizing all patients by computer, you will have a 50% chance of being placed in the opioid-free anesthesia group and a 50% chance of being placed in the opioid control group. The drugs used in the non-opioid anesthesia group included esketamine and dexmetopidine; Patients in the opioid control group were given drugs including sufentanil and remifentanil. Neither the research doctors nor the patients in this study will know which group of patients received which treatment. This is in order to evaluate the results more objectively. Participants who met the criteria were randomly assigned to an opioid-free anesthesia group or an opioid control group. In this study, postoperative recovery quality, incidence of postoperative nausea and vomiting, postoperative pain score and postoperative sleep were compared between the two groups. Once the study is complete, we will advise you which anesthesia protocol to use.

7. What obligations do I have to comply with to participate in the study?

During the study, you are required to do the following: You are obligated to provide an honest medical history and "previous participation in clinical trials," and declare that you have no history of mental disorders.

8. What are the costs involved in participating in the study?

The drugs used in this study are all conventional anesthetic drugs, so they are not within the scope of free use. If you also combine the treatment and examination required for other diseases, and the cost of switching to other treatments because the treatment is not effective, it is also not covered by free.

9. What are the benefits of participating in a study for the treatment of my disease?

Your condition may or may not improve as a result of participating in this study, and the information gained from this study will help determine which treatments are safer and more effective for other patients with similar conditions to yours.

10. Do I have other treatment options?

Participating in this study may or may not improve your health. If you do not participate in the study, you will be anesthetized and rehabilitated according to the usual procedures. The choice of anesthesia protocol will be determined by the anesthesiologist according to your personal situation and clinical experience. We will not record relevant indicators and follow up.

11. What are the possible risks of participating in a study?

This study may cause some adverse reactions and problems for you. The scalp nerve block used in this study is an invasive procedure that may carry the risk of infection at the puncture site, hematoma at the puncture site, and local anesthetic poisoning. Scalp nerve block is a routine clinical operation with mature technique and wide application range. Researchers will standardize operations, reduce risks, and prepare emergency measures to deal with risks as they arise. If you have any discomfort, whether related to this study or not, please notify the study physician immediately and they will be responsible for taking the appropriate treatment for you. If it is indeed related to the research, the sponsor, Beijing Tiantan Hospital Affiliated to Capital Medical University, will bear the treatment costs and provide corresponding economic compensation to you in accordance with relevant national regulations. Even if you have signed this informed consent form, you still retain all your legal rights. Even if you have signed this informed consent form, you still retain all your legal rights.

12. Can I voluntarily opt in and out of the study?

Participation in the study is completely voluntary and you may decline to participate in the study or withdraw from the study at any time during the study without any reason. This decision will not affect the doctor's treatment of you, nor will his or her medical treatment and benefits be affected. In your best interest, your doctor or investigator may discontinue your participation in the study at any time during the study. If you withdraw from this study for any reason, you may also be asked to undergo laboratory tests and a physical examination if the doctor deems it clinically necessary, which is in the interest of protecting your health.

13. What happens if new information becomes available that is relevant to the drug being studied?

Sometimes new information comes to light about the drug being studied. If there is any new information that may affect your willingness to continue to participate in the study, we will notify you in a timely manner and discuss with you whether it is appropriate to continue to participate in the study.

14. How will participating in the study affect my life?

You may find these visits inconvenient, and you can consult the study physician if you have any questions about the tests and procedures used in the study. If you are a fertile woman/man, you will need to use contraception throughout the study period. Consult your study physician to determine what type of contraception to use and for how long. Some forms of contraception were not approved during the study. You may not participate in any other clinical study of any drug or medical device during the study period.

15. Is my personal information confidential?

Your medical records will be kept at the hospital, where researchers, research authorities, ethics committees, supervisors, inspectors, and drug administration inspectors will have access to the subject's original medical records to verify the process and data of the clinical trial. The above personnel have the responsibility to keep your personal information confidential, and will be punished for illegal disclosure. Any confidential matters relating to your identification records will not be used publicly. If clinical trial results are published, your identity will remain confidential. We will make every effort to protect the privacy of your personal medical information to the extent permitted by law. Your name will not be used in any reports.

16. Related consultation

If you have any questions related to this study, please contact Yuxuan Fu on landline 010--59976656 or mobile 18612971557.

If you have any questions related to your own rights or if you would like to report your dissatisfaction and concerns during your participation in this research, please contact the Office of the National Clinical Trials Institute of Beijing Tiantan Hospital, Tel: 010--59975178, or the Ethics Committee Office of Tiantan Hospital, contact Tel: 010--59975692. Email: ttyyirb@163.com.

Subject Consent Statement

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I agree to participate in a clinical study of Opioid-free anaesthesia and postoperative quality of recovery of supratentorial tumour neurosurgery: a randomized controlled trial.

Signing here means:

1. I have read this informed consent form and the researcher has explained the study to me.
2. I have discussed and asked relevant questions about this study, and they have been answered to my satisfaction.
3. I understand that I will be able to obtain compensation from the sponsor in the event of research-related damages.
4. I have plenty of time to make a decision.
5. I voluntarily agree to participate in the clinical research presented in this article.
6. I have been informed of the researcher I should consult during the study.

As described in this informed consent form, I consent to hospital supervision, researchers and other relevant personnel having access to my medical and personal information.

Subject's signature : _____ Date : _____

Name in block letters : _____ Contact number : _____

Signature of legal representative (if any) : _____ Date : _____

The name of the legal representative in block letters : _____

Contact number : _____

Legal representative and patient relationship : _____

Fair Witness Statement :

I was present throughout the informed process, and the contents of the informed consent form and other written materials were accurately explained to the subjects or legal representatives. The subjects or legal representatives fully understood the meaning of the content, and they agreed to participate in the test.

Signature of an impartial witness (if any) : _____ Date : _____

The name of the impartial witness in block letters : _____

Contact number : _____

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Signature of researcher : _____ Date : _____

Name of researcher in block letters : _____

Contact number : _

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Supplement 2 Standard anaesthetic management

1. The intravenous route will be established according to anaesthesia and surgical requirements after admission. Electrocardiograms, heart rate, blood pressure and pulse oxygen saturation will be routinely monitored.

2. Anaesthetic methods: intravenous and inhaled combined anaesthesia. Rocuronium bromide will be added intermittently according to the course of surgery.

3. Mechanical ventilation is initiated with the following parameters: tidal volume, 6–8 mL/kg; respiratory rate, 12–15/min; inspiratory/expiratory ratio, 1:2; inspired oxygen concentration, 60%; and fresh gas flow, 1–2 L/min. The respiratory parameters should be regulated, the patient should be properly hyperventilated, and blood PaCO₂ should be maintained at 30–35 mmHg. After the operation, the sevoflurane was removed, and the fresh gas flow was adjusted to 6 L/min.

4. Hemodynamic management: The anesthesiologist maintains intraoperative blood pressure within 20% of the patient's baseline blood pressure.

5. The BIS is maintained between 40 and 50.

6. All the subjects were given 8 mg of ondansetron intravenously during anaesthesia to prevent postoperative nausea and vomiting. For subjects with severe nausea and vomiting (three or more episodes of vomiting or inability to perform daily activities due to nausea and vomiting), additional medications such as ondansetron may be administered for postoperative remedial antiemetic therapy.

7. Patients with postoperative pain scores ≥ 4 can be given analgesic drugs, such as oxycodone and acetaminophen, for postoperative remedial analgesic treatment.

BMJ Open

Opioid-free anaesthesia and postoperative quality of recovery in patients undergoing supratentorial tumour resection: protocol for a randomised controlled trial

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Opioid-free anaesthesia and postoperative quality of recovery in patients undergoing supratentorial tumour resection: protocol for a randomised controlled trial

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Abstract

Introduction: Opioids play a pivotal role in capable of effectively blocking the pain and stress responses triggered by procedures such as surgery and intubation. However, it should not be overlooked that opioids have numerous side effects, such as respiratory depression, postoperative nausea and vomiting. These effects can raise intracranial pressure, posing a life-threatening risk in neurosurgical patients. Opioid-free anaesthesia can prevent or significantly reduce opioid usage. The aim of this study is to investigate the effect of opioid-free anaesthesia on the quality of recovery in patients undergoing supratentorial tumour resection in neurosurgery.

Methods and analysis: This is a single-centre, randomised controlled clinical trial. A total of 170 patients receiving general anaesthesia will be randomised at a 1:1 ratio into two groups, one receiving opioid-free anaesthesia and the other receiving opioid-based anaesthesia. The primary outcome measure is the quality of recovery-15 score on the second day after surgery. The secondary outcomes include the quality of recovery score on the 5th day, the incidence of nausea and vomiting within 48 hours, the NRS pain score on the second and 5th days, the sleep quality on the second and 5th days after surgery, and the incidence of chronic pain at 3 and 6 months after surgery.

Ethics and dissemination: This study received official approval from the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University, on September 9, 2024 (KY2024-219-02). The findings of this study are intended to be disseminated through publications in international peer-reviewed journals, presentations at national and international academic conferences, and broad distribution via online platforms.

Trial registration: ClinicalTrials.gov, NCT06607029 (September 15, 2024).

Keywords: Esketamine, Multimodal analgesia, Opioid-free anaesthesia, Quality of recovery

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51 **Strengths and limitations of this study**

- 52 ● The randomised controlled study design should provide a high level of evidence.
- 53 ● The QoR-15 score is a validated, multidimensional, and comprehensive assessment of
- 54 postoperative recovery quality, which is easy to implement.
- 55 ● In terms of pain assessment, the study focuses not only on perioperative acute pain but
- 56 also on chronic pain after surgery.
- 57 ● The researchers who perform the postoperative follow-up are unaware of the group
- 58 assignment.
- 59 ● As the study is limited to supratentorial tumour resection, the efficacy of opioid-free
- 60 anaesthesia in broader neurosurgical contexts needs further investigation.

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INTRODUCTION

Opioids play a pivotal role in neurosurgical anaesthesia and are capable of effectively blocking the pain and stress responses triggered by procedures such as surgery and intubation^{1 2}. However, it should not be overlooked that opioids have numerous side effects, such as respiratory depression, postoperative nausea and vomiting. Opioid-induced vomiting and respiratory depression can elevate intracranial pressure, posing a life-threatening risk in neurosurgical patients. Moreover, neurosurgical patients have a high inherent risk of postoperative nausea and vomiting, with an incidence reaching 73%^{3 4}. It is necessary to find a low- or opioid-free anaesthesia strategy that reduces or avoids the use of opioids while achieving the same good perioperative analgesic effects as opioids.

Opioid-free anaesthesia is a multimodal anaesthesia strategy that combines a variety of nonopioid drugs or techniques that act on different nociceptive pathways. The main characteristic of neurosurgery is that pain stimulation occurs during the periods of overhead fixation, cranial opening and closing. Scalp nerve block can effectively block pain during this period and play a role in postoperative analgesia^{5 6}. At present, opioid-free anaesthesia has not been widely used in neurosurgical clinical practice. Few studies have indicated that, compared with opioid anaesthesia, scalp nerve block in combination with the use of dexmedetomidine and acetaminophen opioid-free anaesthesia does not have any disadvantages in terms of the average pain score at 0--12 hours or 0--24 hours after surgery⁷. However, as a retrospective study, this research carries inherent risks of selection bias and data incompleteness, compounded by the limited sample size. Furthermore, this study focused solely on perioperative acute pain without assessing recovery quality.

This study hypothesized that an opioid-free anaesthesia protocol could improve the quality of perioperative recovery in patients undergoing neurosurgical supratentorial tumour resection.

METHODS AND ANALYSIS

Trial setting and eligibility criteria

This trial is a single-centre, randomised, controlled, patient and outcome assessor-blinded trial conducted at Beijing Tiantan Hospital, Capital Medical University. A study coordinator screens elective neurosurgery patients daily to determine eligibility. The inclusion criteria is as follows:

scheduled to undergo craniotomy for supratentorial tumours with general anaesthesia; 18 years≤age≤65 years; American Society of Anaesthesiologists (ASA) physical status of I to III; and sign informed consent (Supplement 1). The exclusion criteria is as follows: body mass index (BMI)≥35 kg/m²; severe hepatic or renal insufficiency; cognitive dysfunction, aphasia or other states that did not cooperate with the assessment; preoperative magnetic resonance imaging of the head showing midline displacement >5 mm⁸; electrophysiological monitoring during surgery; and pregnancy or lactation. The schedules of the activities for the registration, intervention, and assessment of the participants are shown in Table 1 and Figure 1.

Table 1. Schedule of enrollment, interventions, data collection and outcome assessments

| Time point | Operation | | Postoperation follow-up | | | |
|---|---------------|---------------|-------------------------|------------------|---------|---------|
| | Pre-Operation | Dur-Operation | 2d after surgery | 5d after surgery | 3months | 6months |
| Enrollment | | | | | | |
| Eligibility screen | × | | | | | |
| Recruitment | × | | | | | |
| Consent | × | | | | | |
| Randomization and allocation | × | | | | | |
| Intervention | | | | | | |
| Opioid-free anaesthesia group or opioid-based control group | | × | | | | |
| Prerandomization data collection | | | | | | |
| Demographics | × | | | | | |
| Physical examination | × | | | | | |
| Laboratory results | × | | | | | |
| Neurological examination | × | | | | | |

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| Daily data collection | | | | | | |
|--|--|---|---|---|---|---|
| Intraoperative vital signs | | × | | | | |
| The use of antiemetic drugs | | | × | | | |
| The use of analgesic drugs | | | × | × | × | × |
| Laboratory results | | | × | × | | |
| Primary outcome | | | | | | |
| QoR-15 score on the second day after surgery | | | × | | | |
| Secondary outcomes | | | | | | |
| QoR-15 score on the 5th day after surgery | | | | × | | |
| Postoperative nausea and vomiting | | | × | | | |
| NRS pain score | | | × | × | × | × |
| Postoperative sleep quality | | | × | × | | |

QoR, quality of recovery; NRS, numerical rating scale.

Discontinuation or withdrawal of study subjects

Each participant has the right to withdraw from the research at any time for any reason voluntarily, and the researcher may also stop a subject's involvement for any number of reasons, most commonly protocol infractions or safety concerns.

Assignment of interventions

Patients identified as eligible by the study investigator will be randomly assigned to the opioid-free anaesthesia group or the opioid-based control group at a 1:1 ratio. Randomisation is performed on the day of surgery. The table of random numbers is generated by independent

researchers via computer software (SPSS 26.0). In this study, block randomization is adopted, and the block length is 4. The subjects' random results are placed in light-tight envelopes numbered in strict accordance with their enrollment order. The researchers open the envelopes in the order in which they are assigned, ensuring that the assignment information is unpredictable. Before anaesthesia begins, the envelopes are opened by researchers who are unaware of the randomization procedure, and the subjects are assigned to either the opioid-free anaesthesia group or the opioid-based control group. Because of the specificity of the intervention method, the anaesthesiologist knew the grouping of patients, but the surgeon and other members of the medical team did not. The participants and primary outcome evaluators is blinded. The randomisation results are known only when patients experienced a serious adverse event (such as death or life-threatening emergency rescue) that required additional visits.

Interventions

Patients in the opioid-free anaesthesia group will not given opioids during the procedure. Anaesthesia is induced with 1–1.5 mg/kg lidocaine, 1.5–2.5 mg/kg propofol or 0.15–0.3 mg/kg etomidate, and 0.6–0.8 mg/kg rocuronium after loss of consciousness. A visual laryngoscope is placed to expose the epiglottis and glottis, and oral pharyngeal surface anaesthesia is administered with 2% lidocaine. The needles are sprayed evenly in the airway, vocal cords and epiglottic laryngeal surface. Mask ventilation is continued after surface anaesthesia, and endotracheal intubation is performed after lidocaine surface anaesthesia took effect. According to our local practices, anaesthesia is maintained with a 0.3–0.6 minimum alveolar concentration (MAC) of sevoflurane or desflurane combined with 0.12 mg/kg/h esketamine, 0.4–0.6 µg/kg/h dexmedetomidine, and 2–4 mg/kg/h propofol. The anaesthesiologist may adjust the drug type and dosage (without opioids) according to the specific situation of each subject, and all medications must be recorded in detail. If there are any adverse events associated with esketamine and dexmetopidine during the procedure, such as severe bradycardia, the medication should be discontinued, and opioids may be appropriately administered to ensure a smooth operation. If patients in the opioid-free anaesthesia group have strong pain stimulation during surgery, resulting in persistent tachycardia or elevated blood pressure, opioid analgesia

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can be appropriately administered to ensure stable haemodynamics.

For patients in the opioid-based control group, 0.3–0.5 µg/kg sufentanil, 1.5–2.5 mg/kg propofol or 0.15–0.3 mg/kg etomidate, and 0.6–0.8 mg/kg rocuronium are used for anaesthesia induction. According to our local practices, anaesthesia is maintained with a 0.3–0.6 minimum alveolar concentration (MAC) of sevoflurane or desflurane combined with 0.05–0.2 µg/kg/min of remifentanyl and 2–4 mg/kg/h propofol. Sufentanil is administered intermittently at 0.1 µg/kg as required by surgery. The anaesthesiologist can adjust the drug type and dosage according to the specific situation of each subject, and all medications should be recorded in detail.

Standardized anaesthesia management

Standardized anaesthesia management is adopted for all patients. The intravenous route is established according to anaesthesia and surgical requirements after admission. Electrocardiograms, heart rate, blood pressure and pulse oxygen saturation are routinely monitored. After induction of anaesthesia, bilateral scalp nerve block is performed with 0.5% ropivacaine. The scalp nerve blocks included the supraorbital nerve, supratrochlear nerve, auriculotemporal nerve, zygomaticotemporal nerve, major occipital nerve and minor occipital nerve. The nerve block site is selected according to the location of the surgical incision and head nail, and 2–3 ml of local anaesthetic is injected into each block site. Scalp nerve blocks are performed by an anaesthesiologist under ultrasound guidance. Dexamethasone is not used as a local anaesthetic for nerve block. Rocuronium bromide is added intermittently according to the course of surgery. The respiratory parameters should be regulated, the patient should be properly hyperventilated, and blood PaCO₂ should be maintained at 30–35 mmHg. The anaesthesiologist, on the basis of the patient's response to the drug, adjusts the dose of the sedative drugs (propofol and sevoflurane) to ensure that the BIS is between 40 and 50. During surgery, anaesthesiologists do not routinely administer steroids. Steroid therapy is only continued perioperatively for patients who require ongoing steroid treatment due to pre-existing medical conditions. After the operation, the sevoflurane is removed, and the fresh gas flow is adjusted to 6 L/min. All the subjects are given 8 mg of ondansetron intravenously during anaesthesia to prevent postoperative nausea and vomiting. For subjects with severe nausea and vomiting (three or more episodes of vomiting or inability to perform daily activities due to

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nausea and vomiting), additional medications such as ondansetron may be administered for postoperative remedial antiemetic therapy. Patients with postoperative pain scores ≥ 4 can be given analgesic drugs, such as oxycodone and acetaminophen, for postoperative remedial analgesic treatment, and all drugs should be recorded in detail (Supplement 2). If intraoperative blood loss exceeds 40% of the blood volume or if there are other adverse events that threaten the life of the patient, the study is terminated, and opioids can be given as needed. The anaesthesiologist should actively handle the situation according to the situation and record the processing process.

Primary outcome

The primary outcome measure is the quality of recovery-15 (QoR-15) score on the second day after surgery. The QoR-15 scale is used to evaluate the postoperative recovery of patients in five dimensions: pain, physical comfort, physical independence, psychological support and emotional state⁹. Each item is scored on a 10-point scale ranging from 0 (worst recovery) to 150 (best recovery)⁹. According to the results of previous meta-analyses, a change in the QoR-15 scale score to 6 points is considered to be clinically significant¹⁰⁻¹².

Secondary outcomes

The secondary outcomes in this study included the QoR-15 score on the 5th day after surgery; the incidence of nausea and vomiting within 48 hours after surgery (including nausea, retching, or vomiting episodes); the NRS (Numerical Rating Scale) pain score on the second and 5th days after surgery; the sleep quality on the second and 5th days after surgery; and the incidence of chronic pain at 3 and 6 months after surgery¹³. Chronic pain is defined as pain that lasts longer than 3 months¹³. Perioperative sleep quality is assessed via the Athens Insomnia Scale (AIS). Safety indicators, including the incidence of intraoperative bradycardia (heart rate < 60 bpm), tachycardia (heart rate > 100 bpm), hypertension (more than 30% of baseline blood pressure and requiring drug intervention), hypotension (less than 30% of baseline blood pressure and requiring drug intervention) and postoperative intracranial hemorrhage, should also be considered. For patients who develop postoperative intracranial hemorrhage, we will document the following parameters: clinical manifestations, hemorrhage volume (measured in milliliters),

management strategies (including the need for surgical intervention and/or blood transfusion), and clinical outcomes.

Data collection

At patient enrollment, the researchers collected the demographic and baseline characteristics of the patients. All patients are assessed using the Apfel score. Patients' vital signs, anaesthetic administration, fluid volume, blood loss, and urine volume are recorded intraoperatively. The quality of recovery, pain score, sleep quality, postoperative nausea and vomiting, postoperative complications and adverse events are recorded during postoperative follow-up. Pain scores are obtained via telephone at 3 and 6 months after surgery. The researchers also collected information on the percentage of patients in the opioid-free anaesthesia group who used opioids. Considering the influence of the pathological type of a tumour on patient prognosis, researchers should also collect the pathological results of patients after surgery. All participants enrolled in the randomization are followed up until six months after surgery. To promote the participation of the subjects in this study and ensure the integrity of the data, we collect the contact information of their families in addition to the subjects for follow-up after discharge. All patients in our centre use electronic versions of medical records and anaesthesia sheets. In this study, a paper case report form is used to record the information of the participants.

Data management

Raw data for all patients are collected via paper case report forms specially designed by the researchers and placed in dedicated lockers with locks. The paper case report form for this study is destroyed three years after the end of the study. The electronic data of this study are stored encrypted after hiding personal information. Only leading researchers have access to the electronic database. All researchers involved in this study strictly abided by the rules of professional confidentiality and keep all personal information of patients confidential.

Sample size

According to unpublished data from a preliminary study of 20 patients in our centre, the QoR-15 score of neurosurgery patients on the second day after surgery was 109 ± 14 . Changes of up

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to 6 points on the QoR-15 scale are considered clinically significant¹⁰⁻¹². Finally, with the use of the PASS-15, a total of 170 patients are needed to detect differences in the primary outcome with 80% power and a two-sided alpha of 0.05, allowing for a 5% loss to follow-up.

Statistical methods

All patients enrolled in the randomisation process, including those who discontinued the study due to intraoperative adverse events such as bleeding, are included in a modified intentionality analysis. The primary outcome will be analysed via modified intentionality analysis and per-protocol analysis. All analyses will be conducted by researchers who are unaware of the intervention. The continuous variables used in this study are tested for normality via the Kolmogorov–Smirnov test. Data conforming to a normal distribution will be expressed as the mean ± standard deviation, and nonnormally distributed data will be expressed as the median and interquartile range. The t test will be used for continuous variables that conform to a normal distribution, and the Mann–Whitney U test will be used for continuous variables that do not conform to a normal distribution. Categorical variables are expressed as percentages and are analysed via chi-square tests, corrected chi-square tests, or Fisher’s exact tests. Intraoperative haemodynamic parameters, including systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate, will be compared between the two groups via repetitive measurement deviation analysis. For the missing data, the last observation and the worst-case imputation scenarios are used as the main interpolation methods. A P value of 0.05 or less (double-tailed letter level) is considered statistically significant. No interim analysis is planned for this study.

Data safety and monitoring

The accuracy and security of all the data are governed by an appointed data monitoring committee. The Data Safety Monitoring Board is independent of the researchers and includes an anaesthesiologist, a neurosurgeon, and a biostatistician. The data monitoring committee will review the contents of the database every six months to ensure that all the data are collected accurately and in a timely manner. The principal investigator regularly monitored and tracked the anaesthesiologist's compliance with the protocol.

Serious adverse events

An adverse event is defined as an adverse event or worsening of a preexisting medical condition that occurred during the study period, whether or not it is related to the intervention in this study. All adverse events associated with this study will be closely monitored until the adverse events are resolved and the condition stabilizes. Adverse events are reported to the research department immediately after they occur, and the severity of the adverse events is determined by the principal investigator. In addition, the principal investigator should report this information to the Ethics Committee (IRB) within 24 hours. The Data Monitoring Board will be responsible for monitoring clinical safety and reviewing all adverse events reported to the IRB to determine the risks and benefits of the study. If a patient's health is compromised as a result of participation in this study, we will be responsible for receiving appropriate treatment. Beijing Tiantan Hospital will pay for the treatment of patients in accordance with relevant national regulations and pay corresponding financial compensation to patients.

Patients and public involvement

Patients and the public were not directly consulted during the formulation of the research questions or outcome measurements, and did not participate in the study's design, recruitment, or implementation. The study's results will be disseminated to all study participants via their preferred method.

ETHICS AND DISSEMINATION

Research ethics approval and consent process

This study is performed in accordance with the principles of the Declaration of Helsinki. Prior to the study, the study was approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (KY2024-219-02). The investigator will present the study to the patient or his/her legal representative the day before the procedure, and the patient or his/her legal representative will sign a written informed consent form on the day of the procedure. This protocol is reported in accordance with the requirements of the SPIRIT guidelines.

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Protocol amendments

The principal investigator has the right to modify the study protocol. The principal investigator will need to communicate with the research department before implementing the revised protocol. Changes to the study protocol will be subject to approval by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University.

Confidentiality and access to data

The randomisation results of this study will be stored in an opaque envelope that is coded and identified according to the order in which patients are enrolled. All the subjects' paper copies will be stored in a locked cabinet. The electronic data of the subject are stored encrypted after the personal information is concealed. Only the principal investigator has access to the final database.

Dissemination policy

The findings of this study are intended to be disseminated through publications in international peer-reviewed journals, presentations at national and international academic conferences, and broad distribution via online platforms. The findings will also be disseminated to all study participants at the end of the study.

DISCUSSION

This randomised controlled study is investigating whether an opioid-free anaesthesia regimen could improve the quality of perioperative recovery in neurosurgery patients. Opioids are a double-edged sword that are effective analgesics but also may cause respiratory depression, nausea and vomiting, hyperalgesia, immune suppression, skin itching, myoclonus and other adverse reactions. These side effects can lead to delayed recovery, longer hospital stays, and increased health care costs^{2 14}. Enhanced recovery after surgery (ERAS) recommends reducing perioperative opioid use or adopting an opioid-free anaesthesia regimen to improve the quality of patients' perioperative recovery^{15 16}. Opioid use disorder is becoming a global public health crisis. Nearly 50,000 people in the United States die each year from opioid-related causes, and excessive perioperative opioid prescription has been identified as a significant cause¹⁷. In

addition, 2%-6% of patients who had no previous opioid addiction exhibited continued opioid use after surgery¹⁸.

Given the limited effects of surface anaesthesia and nerve blocking, we used a combination of other nonopioid analgesics, such as dexmedetomidine and esketamine, during the perioperative period. Dexmedetomidine is a highly selective α_2 -adrenergic receptor agonist with sedative and analgesic effects¹⁹⁻²¹. The analgesic effect of dexmedetomidine is different from that of opioids, and it can inhibit inflammation and oxidative stress through a variety of pathways, producing neuroprotective effects²⁰. In addition, dexmedetomidine reduces injurious input and delivery by activating α_2 receptors in the dorsal horn of the spinal cord²². Esketamine is an S-enantiomer of racemic ketamine and has a higher affinity for the N-methyl-D-aspartate receptor than does ketamine²³. Esketamine has excellent analgesic effects and is increasingly used for perioperative pain management²³⁻²⁶. Remifentanyl is an ultra-short-acting μ -opioid receptor agonist characterized by rapid onset, swift metabolism by nonspecific esterases, and minimal accumulation. Therefore, in the opioid control group, we selected remifentanyl for anaesthetic maintenance to facilitate early neurological assessment²⁷.

At present, opioid-free anaesthesia is not widely used in neurosurgical clinical practice. A previous study validated the feasibility of opioid-free anaesthesia in neurosurgical patients⁷. The study prospectively enrolled six patients for craniotomy via opioid-free anaesthesia. These six patients were matched to 18 patients who were anaesthetized with opioids by age, sex, incision length, and incision location⁷. Scalp nerve block in combination with the use of dexmedetomidine and acetaminophen opioid-free anaesthesia does not have any disadvantages in terms of the average pain score at 0--12 hours or 0--24 hours after surgery⁷. Nevertheless, the study was very small and lacked a comparator group.

In addition to focusing on the analgesic effects of opioid-free anaesthesia strategies in neurosurgical patients, this study focused on the quality of perioperative recovery. The primary outcome measure is the quality of recovery-15 (QoR-15) score on the second day after surgery. The QoR-15 scale, a tool used to evaluate recovery quality during the perioperative period, has the advantages of strong effectiveness and a sensitive response¹⁰. Opioid-free anaesthesia has been widely used in a variety of nonneurosurgical procedures to improve the quality of patients' perioperative recovery^{28,29}. Two recently published high-quality meta-analyses have both found

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that opioid-free anaesthesia can improve the quality of postoperative recovery (especially the QoR-40 score within 24 hours after surgery), and can reduce the incidence of postoperative nausea and vomiting. However, when the QoR-15 score was used to evaluate the quality of recovery, the two studies showed inconsistent results, which might be related to insufficient sample size or high heterogeneity^{17 30}. The SOFA study found that patients receiving opioid-free anaesthesia showed slight improvements in the quality of recovery at 24 hours, 48 hours, and 72 hours after surgery, but these differences did not fully reach the threshold of clinical significance³¹. Although this study included various types of surgeries, it did not cover the field of neurosurgery³¹.

This study has several limitations. First, due to the nature of the intervention, the anaesthesiologists are aware of the group allocations, which may have introduced bias. To mitigate this, intraoperative management strictly adhered to a standardized anaesthesia protocol, and the anaesthesiologists responsible for postoperative follow-up are blinded to group assignments. Second, as a single-centre study involving only patients undergoing supratentorial tumour resection, the efficacy of opioid-free anaesthesia in other neurosurgical populations remains uncertain and warrants further investigation.

In conclusion, the successful completion of this trial and the validation of its underlying hypotheses will provide evidence for the use of opioid-free anaesthesia in neurosurgery patients. If the results are positive, new perioperative management strategies may be developed for neurosurgical patients.

Trial status

This clinical study is currently in the recruitment phase. The study recruited the first patient on October 21, 2024, and the estimated study completion date is October 31, 2025.

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Contributors: YF drafted the manuscript for this protocol. YF, YZ, YC, YW, TW, YL and RH initiated the study design and refined the research protocol. YY provided statistical analysis guidance. YF, YZ, YC, YW, TW, YL and YY contributed to data collection and manuscript revision. RH is the grant holder and the corresponding author. All the authors have read and approved the final manuscript. Ruquan Han is the guarantor.

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Competing interests: The authors have no competing interests to disclose.

Data availability statement: The deidentified participant data from this study can be made available to researchers upon reasonable request with approval by the corresponding author (Dr. Ruquan Han, ruquan.han@ccmu.edu.cn) immediately after publication of the study results. Requests should provide a formal protocol for database use that has received ethics approval.

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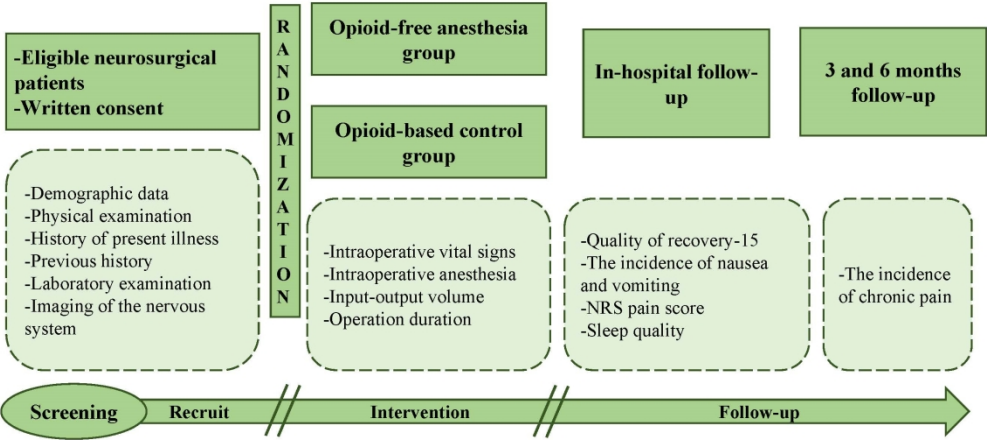
495 **FIGURE LEGEND**

496 **Figure 1.** Study implementation flowchart

497 NRS, Numerical Rating Scale.

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Informed consent

Name of the research scheme: Opioid-free anaesthesia and
postoperative quality of recovery of supratentorial tumour
neurosurgery: a randomized controlled trial

Applicant: Beijing Tiantan Hospital, Capital Medical University

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Dear patient,

We invite you to participate in the study " Opioid-free anaesthesia and postoperative quality of recovery of supratentorial tumour neurosurgery: a randomized controlled trial " approved by Beijing Tiantan Hospital Affiliated to Capital Medical University. The study will be conducted at Beijing Tiantan Hospital affiliated to Capital Medical University, and an estimated 170 participants will voluntarily participate. Participation in this study is voluntary. Some of the content covered in this paper is subject to regulatory requirements and has been reviewed and approved by the Ethics Committee of Beijing Tiantan Hospital affiliated to Capital Medical University in order to protect the rights and interests of the patients participating in the study.

1. Why was this study conducted?

Background: Opioids are the most effective drugs for the treatment of pain, and are an important part of general anesthesia, and are the most widely used anti-nociceptive drugs in the perioperative period. Opioids have many side effects, such as constipation, urinary retention, itchy skin, respiratory depression, and postoperative nausea and vomiting. These side effects can lead to delayed recovery, longer hospital stays, and increased health care costs. In recent years, with the concept of rapid rehabilitation surgery after surgery, a new perioperative analgesia strategy model is called opioid-free anesthesia. Rapid rehabilitation surgery theory emphasizes reducing perioperative opioid use to improve the quality of patients' perioperative recovery.

Purpose: We conducted this randomized controlled study to provide clinical evidence for the efficacy and safety of opioid-free anesthesia in neurosurgical patients.

2. How many people will participate in the study?

About 170 people will participate in the study at Beijing Tiantan Hospital affiliated to Capital Medical University, and 170 people are planned to participate in the study.

3. Who are selected to participate in the study?

Our inclusion criteria included: 18 years \leq age \leq 65 years; American Society of Anesthesiologists (ASA) physical status of I to III; and signed informed consent. Whether or not you can participate in the study needs to be examined by a doctor.

4. Who should not participate in the study?

Our exclusion criteria included: patients with a body mass index (BMI) \geq 35 kg/m²; patients with severe hepatic and renal insufficiency; patients with cognitive dysfunction, aphasia or other states that did not cooperate with the assessment; patients with preoperative magnetic resonance imaging of the head showing midline displacement >5 mm⁷; patients who underwent electrophysiological monitoring during surgery; and pregnant or lactating patients. If you are in any of the above criteria, you are not included in this study.

5. How long will the study last?

The study will last for 2 years. If you participate in the study, you will need to collect some medical information from the date of enrollment to the time of discharge, and follow up until the fifth day after surgery. You can opt out of the study at any time without forfeiting any benefits you would otherwise have received. However, if during the study you decide to withdraw from the study, we encourage you to consult with your doctor first. In view of your security concerns, it is possible that a relevant check will be conducted after the exit.

6. How was the study conducted?

If you are willing to participate in the study, your doctor will review your medical history, ask about past and current therapeutic medications, and undergo a routine preoperative

examination to further confirm your suitability for participation in the study. By randomizing all patients by computer, you will have a 50% chance of being placed in the opioid-free anesthesia group and a 50% chance of being placed in the opioid control group. The drugs used in the non-opioid anesthesia group included esketamine and dexmetopidine; Patients in the opioid control group were given drugs including sufentanil and remifentanil. Neither the research doctors nor the patients in this study will know which group of patients received which treatment. This is in order to evaluate the results more objectively. Participants who met the criteria were randomly assigned to an opioid-free anesthesia group or an opioid control group. In this study, postoperative recovery quality, incidence of postoperative nausea and vomiting, postoperative pain score and postoperative sleep were compared between the two groups. Once the study is complete, we will advise you which anesthesia protocol to use.

7. What obligations do I have to comply with to participate in the study?

During the study, you are required to do the following: You are obligated to provide an honest medical history and "previous participation in clinical trials," and declare that you have no history of mental disorders.

8. What are the costs involved in participating in the study?

The drugs used in this study are all conventional anesthetic drugs, so they are not within the scope of free use. If you also combine the treatment and examination required for other diseases, and the cost of switching to other treatments because the treatment is not effective, it is also not covered by free.

9. What are the benefits of participating in a study for the treatment of my disease?

Your condition may or may not improve as a result of participating in this study, and the information gained from this study will help determine which treatments are safer and more effective for other patients with similar conditions to yours.

10. Do I have other treatment options?

Participating in this study may or may not improve your health. If you do not participate in the study, you will be anesthetized and rehabilitated according to the usual procedures. The choice of anesthesia protocol will be determined by the anesthesiologist according to your personal situation and clinical experience. We will not record relevant indicators and follow up.

11. What are the possible risks of participating in a study?

This study may cause some adverse reactions and problems for you. The scalp nerve block used in this study is an invasive procedure that may carry the risk of infection at the puncture site, hematoma at the puncture site, and local anesthetic poisoning. Scalp nerve block is a routine clinical operation with mature technique and wide application range. Researchers will standardize operations, reduce risks, and prepare emergency measures to deal with risks as they arise. If you have any discomfort, whether related to this study or not, please notify the study physician immediately and they will be responsible for taking the appropriate treatment for you. If it is indeed related to the research, the sponsor, Beijing Tiantan Hospital Affiliated to Capital Medical University, will bear the treatment costs and provide corresponding economic compensation to you in accordance with relevant national regulations. Even if you have signed this informed consent form, you still retain all your legal rights. Even if you have signed this informed consent form, you still retain all your legal rights.

12. Can I voluntarily opt in and out of the study?

Participation in the study is completely voluntary and you may decline to participate in the study or withdraw from the study at any time during the study without any reason. This decision will not affect the doctor's treatment of you, nor will his or her medical treatment and benefits be affected. In your best interest, your doctor or investigator may discontinue your participation in the study at any time during the study. If you withdraw from this study for any reason, you may also be asked to undergo laboratory tests and a physical examination if the doctor deems it clinically necessary, which is in the interest of protecting your health.

13. What happens if new information becomes available that is relevant to the drug being studied?

Sometimes new information comes to light about the drug being studied. If there is any new information that may affect your willingness to continue to participate in the study, we will notify you in a timely manner and discuss with you whether it is appropriate to continue to participate in the study.

14. How will participating in the study affect my life?

You may find these visits inconvenient, and you can consult the study physician if you have any questions about the tests and procedures used in the study. If you are a fertile woman/man, you will need to use contraception throughout the study period. Consult your study physician to determine what type of contraception to use and for how long. Some forms of contraception were not approved during the study. You may not participate in any other clinical study of any drug or medical device during the study period.

15. Is my personal information confidential?

Your medical records will be kept at the hospital, where researchers, research authorities, ethics committees, supervisors, inspectors, and drug administration inspectors will have access to the subject's original medical records to verify the process and data of the clinical trial. The above personnel have the responsibility to keep your personal information confidential, and will be punished for illegal disclosure. Any confidential matters relating to your identification records will not be used publicly. If clinical trial results are published, your identity will remain confidential. We will make every effort to protect the privacy of your personal medical information to the extent permitted by law. Your name will not be used in any reports.

16. Related consultation

If you have any questions related to this study, please contact Yuxuan Fu on landline 010--59976656 or mobile 18612971557.

If you have any questions related to your own rights or if you would like to report your dissatisfaction and concerns during your participation in this research, please contact the Office of the National Clinical Trials Institute of Beijing Tiantan Hospital, Tel: 010--59975178, or the Ethics Committee Office of Tiantan Hospital, contact Tel: 010--59975692. Email: ttyyirb@163.com.

Subject Consent Statement

I agree to participate in a clinical study of Opioid-free anaesthesia and postoperative quality of recovery of supratentorial tumour neurosurgery: a randomized controlled trial.

Signing here means:

1. I have read this informed consent form and the researcher has explained the study to me.
2. I have discussed and asked relevant questions about this study, and they have been answered to my satisfaction.
3. I understand that I will be able to obtain compensation from the sponsor in the event of research-related damages.
4. I have plenty of time to make a decision.
5. I voluntarily agree to participate in the clinical research presented in this article.
6. I have been informed of the researcher I should consult during the study.

As described in this informed consent form, I consent to hospital supervision, researchers and other relevant personnel having access to my medical and personal information.

Subject's signature : _____ Date : _____

Name in block letters : _____ Contact number : _____

Signature of legal representative (if any) : _____ Date : _____

The name of the legal representative in block letters : _____

Contact number : _____

Legal representative and patient relationship : _____

Fair Witness Statement :

I was present throughout the informed process, and the contents of the informed consent form and other written materials were accurately explained to the subjects or legal representatives. The subjects or legal representatives fully understood the meaning of the content, and they agreed to participate in the test.

Signature of an impartial witness (if any) : _____ Date : _____

The name of the impartial witness in block letters : _____

Contact number : _____

Signature of researcher : _____ Date : _____

Name of researcher in block letters : _____

Contact number : _

For peer review only

Supplement 2 Standard anaesthetic management

1. The intravenous route will be established according to anaesthesia and surgical requirements after admission. Electrocardiograms, heart rate, blood pressure and pulse oxygen saturation will be routinely monitored.
2. Anaesthetic methods: intravenous and inhaled combined anaesthesia. Rocuronium bromide will be added intermittently according to the course of surgery.
3. Mechanical ventilation is initiated with the following parameters: tidal volume, 6–8 mL/kg; respiratory rate, 12–15/min; inspiratory/expiratory ratio, 1:2; inspired oxygen concentration, 60%; and fresh gas flow, 1–2 L/min. The respiratory parameters should be regulated, the patient should be properly hyperventilated, and blood PaCO₂ should be maintained at 30–35 mmHg. After the operation, the sevoflurane was removed, and the fresh gas flow was adjusted to 6 L/min.
4. Hemodynamic management: The anesthesiologist maintains intraoperative blood pressure within 20% of the patient's baseline blood pressure.
5. The BIS is maintained between 40 and 50.
6. All the subjects were given 8 mg of ondansetron intravenously during anaesthesia to prevent postoperative nausea and vomiting. For subjects with severe nausea and vomiting (three or more episodes of vomiting or inability to perform daily activities due to nausea and vomiting), additional medications such as ondansetron may be administered for postoperative remedial antiemetic therapy.
7. Patients with postoperative pain scores ≥ 4 can be given analgesic drugs, such as oxycodone and acetaminophen, for postoperative remedial analgesic treatment.

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