BMJ Open

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

Yuxuan Fu ,[1] Yang Zhou,[1] Yidan Cui,[2] Youxuan Wu,[1] Tianyuan Wang,[1] Yang Li,[1] Yun Yu ,[1] Ruquan Han [1]

To cite: Fu Y, Zhou Y, Cui Y, *et al* . Opioid-free anaesthesia and postoperative quality of recovery in patients undergoing supratentorial tumour resection: protocol for a randomised controlled trial. *BMJ Open* 2025;**15**:e099864. doi:10.1136/bmjopen-2025-099864

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2025-099864).

Received 27 January 2025
Accepted 25 April 2025

[1]Department of Anesthesiology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[2]Beijing Nuclear Industry Hospital, Beijing, China

Correspondence to
Dr Ruquan Han;
ruquan.han@gmail.com

ABSTRACT

Introduction Opioids play a pivotal role in being 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 in 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 fifth day, the incidence of nausea and vomiting within 48 hours, the NRS Pain Score on the second and fifth days, the sleep quality on the second and fifth days after surgery, and the incidence of chronic pain at 3 months 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 9 September 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 number ClincalTrials.gov, NCT06607029 (15 September 2024)

STRENGTHS AND LIMITATIONS OF THIS STUDY

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

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-anaesthesia 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 non-opioid 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 surgery.[7] 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 hypothesised 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 are as follows: scheduled to undergo craniotomy for supratentorial tumours with general anaesthesia; 18 years ≤ age ≤ 65 years; American Society of Anesthesiologists physical status of I to III; and signed informed consent (online supplemental 1). The exclusion criteria are as follows: body mass index ≥35 kg/m^2; severe hepatic or renal insufficiency; cognitive dysfunction, aphasia or other states that did not cooperate with the assessment; preoperative MRI of the head showing midline displacement >5 mm;[8] 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.

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 in 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 V.26.0). In this study, block randomisation is adopted, and the block length is 4. The subjects' random results are placed in light-tight envelopes numbered in strict accordance with their enrolment 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 randomisation 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 are 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 be 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 takes 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/hour esketamine, 0.4–0.6 µg/kg/hour dexmedetomidine, and 2–4 mg/kg/hour 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 dexmetomidine 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 are used for anaesthesia induction. According to our local practices, anaesthesia is maintained with a 0.3–0.6 MAC of sevoflurane or desflurane combined with 0.05–0.2 µg/kg/min of remifentanil and 2–4 mg/kg/hour 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.

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

Time point	Operation		Postoperation follow-up			
	Preoperation	During operation	2 days after surgery	5 days after surgery	3 months	6 months
Enrolment						
Eligibility screen	✖					
Recruitment	✖					
Consent	✖					
Randomisation and allocation	✖					
Intervention						
Opioid-free anaesthesia group or opioid-based control group		✖				
Prerandomisation 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						
QoR-15 Score on the second day after surgery			✖			
Secondary outcomes						
QoR-15 Score on the fifth day after surgery				✖		
Postoperative nausea and vomiting			✖			
NRS Pain Score			✖	✖	✖	✖
Postoperative sleep quality			✖	✖		

NRS, Numerical Rating Scale; QoR, quality of recovery.

Standardised anaesthesia management

Standardised anaesthesia management is adopted for all patients. The intravenous route is established according to anaesthesia and surgical requirements after admission. ECGs, 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 partial pressure of carbon dioxide in arterial blood ($PaCO_2$) should be maintained at 30–35 mm Hg. 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 bispectral index (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

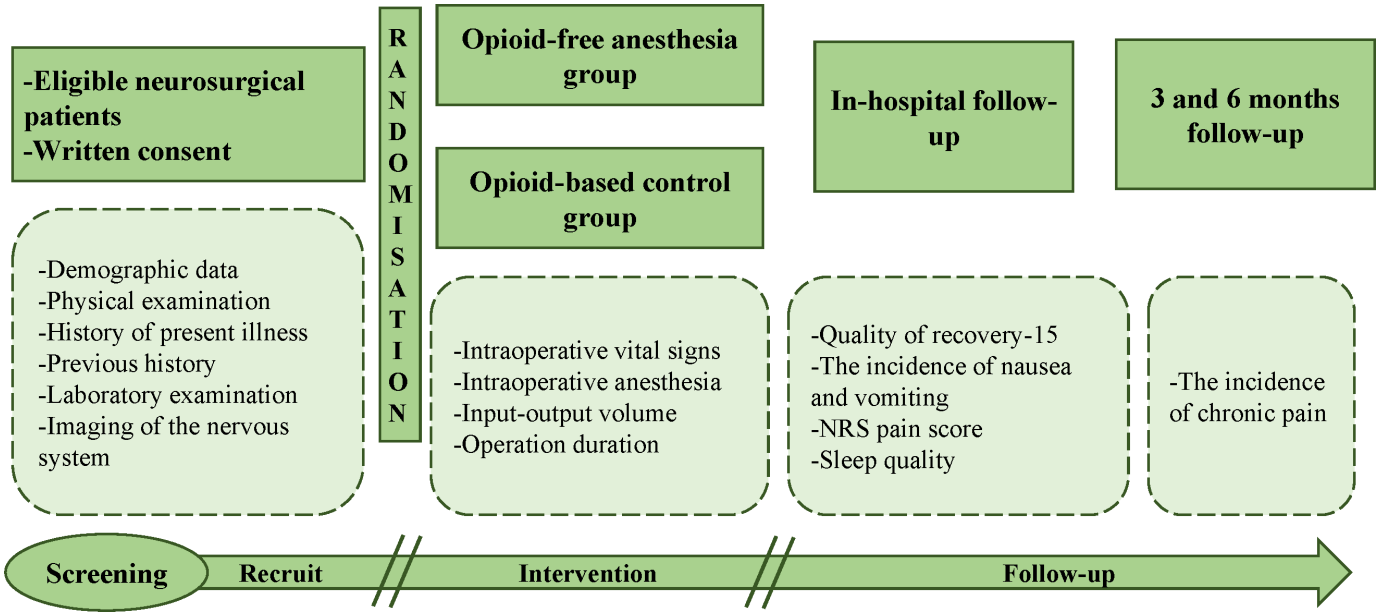

Figure 1 Study implementation flow chart. NRS, Numerical Rating Scale.

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 (online supplemental 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 state.[9] 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 significant.[10–12]

Secondary outcomes

The secondary outcomes in this study included the QoR-15 Score on the fifth day after surgery; the incidence of nausea and vomiting within 48 hours after surgery (including nausea, retching or vomiting episodes); the Numerical Rating Scale Pain Score on the second and fifth days after surgery; the sleep quality on the second and fifth days after surgery; and the incidence of chronic pain at 3 months and 6 months after surgery.[13] Chronic pain is defined as pain that lasts longer than 3 months.[13] Perioperative sleep quality is assessed via the Athens Insomnia Scale. 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 haemorrhage, should also be considered. For patients who develop postoperative intracranial haemorrhage, we will document the following parameters: clinical manifestations, haemorrhage volume (measured in millilitres), management strategies (including the need for surgical intervention and/or blood transfusion), and clinical outcomes.

Data collection

At patient enrolment, 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 months 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 randomisation are followed up until 6 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 3 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 kept 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 significant.[10–12] Finally, with the use of the Power Analysis and Sample Size-15 (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±SD, and non-normally distributed data will be expressed as the median and IQR. 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 χ^2 tests, corrected χ^2 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 value of p=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 6 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 pre-existing 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 stabilises. 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 (Institutional Review Board, 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 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 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 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 healthcare costs.[2 14] Enhanced recovery after surgery 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 50000 people in the USA die each year from opioid-related causes, and excessive perioperative opioid prescription has been identified as a significant cause.[17] In addition, 2%–6% of patients who had no previous opioid addiction exhibited continued opioid use after surgery.[18]

Given the limited effects of surface anaesthesia and nerve blocking, we used a combination of other non-opioid analgesics, such as dexmedetomidine and esketamine, during the perioperative period. Dexmedetomidine is a highly selective α_2-adrenergic receptor agonist with sedative and analgesic effects.[19–21] 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 effects.[20] In addition, dexmedetomidine reduces injurious input and delivery by activating α_2 receptors in the dorsal horn of the spinal cord.[22] Esketamine is an S-enantiomer of racemic ketamine and has a higher affinity for the N-methyl-D-aspartate receptor than does ketamine.[23] Esketamine has excellent analgesic effects and is increasingly used for perioperative pain management.[23–26] Remifentanil is an ultra-short-acting μ-opioid receptor agonist characterised by rapid onset, swift metabolism by non-specific esterases, and minimal accumulation. Therefore, in the opioid control group, we selected remifentanil for anaesthetic maintenance to facilitate early neurological assessment.[27]

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 patients.[7] The study prospectively enrolled six patients for craniotomy via opioid-free anaesthesia. These 6 patients were matched to 18 patients who were anaesthetised with opioids by age, sex, incision length and incision location.[7] 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.[7] Nevertheless, the sample size of this study was very small, and there was a risk of bias.

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 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 response.[10] Opioid-free anaesthesia has been widely used in a variety of non-neurosurgical procedures to improve the quality of patients' perioperative recovery.[28 29] Two recently published high-quality meta-analyses have both found 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] A large randomised controlled 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 significance.[31] Although this study included various types of surgeries, it did not cover the field of neurosurgery.[31]

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 standardised 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 21 October 2024, and the estimated study completion date is 31 October 2025.

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. RH is the guarantor.

Funding This study is funded by Clinical Medicine Development of Special Funding Support (ZYLX201708; DFL20180502)

Competing interests None declared.

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

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Yuxuan Fu http://orcid.org/0009-0004-1718-2362
Yun Yu http://orcid.org/0000-0001-6580-9554
Ruquan Han http://orcid.org/0000-0003-4335-8670

REFERENCES

1 Feenstra ML, Jansen S, Eshuis WJ, *et al*. Opioid-free anesthesia: A systematic review and meta-analysis. *J Clin Anesth* 2023;90:111215.
2 Ferreira P-RC, De Oliveira RIP, Vaz MD, *et al*. Opioid-Free Anaesthesia Reduces Complications in Head and Neck Microvascular Free-Flap Reconstruction. *JCM* 2023;12:6445.
3 Ferreira MY, Barbosa GS, Neto J da C, *et al*. Placebo-controlled efficacy of 5-HT3 antagonists for postoperative nausea and vomiting prophylaxis in supratentorial craniotomies: A systematic review and comparative meta-analysis of randomized clinical trials. *Clin Neurol Neurosurg* 2024;246:108569.
4 Uribe AA, Stoicea N, Echeverria-Villalobos M, *et al*. Postoperative Nausea and Vomiting After Craniotomy: An Evidence-based Review of General Considerations, Risk Factors, and Management. *J Neurosurg Anesthesiol* 2021;33:212–20.
5 Tonković D, Bandić Pavlović D, Baronica R, *et al*. Regional Anaesthesia for Neurosurgery. *Acta Clin Croat* 2019;58:48–52.
6 Papangelou A, Radzik BR, Smith T, *et al*. A review of scalp blockade for cranial surgery. *J Clin Anesth* 2013;25:150–9.
7 McCullough IL, Shteamer JW, Erwood AM, *et al*. Opioid-Free Anesthesia for Craniotomy. *J Neurosurg Anesthesiol* 2023;35:80–5.
8 Fraga M, Rama-Maceiras P, Rodiño S, *et al*. The Effects of Isoflurane and Desflurane on Intracranial Pressure, Cerebral Perfusion Pressure, and Cerebral Arteriovenous Oxygen Content Difference in Normocapnic Patients with Supratentorial Brain Tumors. *Anesthesiology* 2003;98:1085–90.
9 Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology* 2013;118:1332–40.
10 Myles PS, Shulman MA, Reilly J, *et al*. Measurement of quality of recovery after surgery using the 15-item quality of recovery scale: a systematic review and meta-analysis. *Br J Anaesth* 2022;128:1029–39.
11 Myles PS, Myles DB, Galagher W, *et al*. Minimal Clinically Important Difference for Three Quality of Recovery Scales. *Anesthesiology* 2016;125:39–45.
12 Myles PS, Myles DB. An Updated Minimal Clinically Important Difference for the QoR-15 Scale. *Anesthesiology* 2021;135:934–5.
13 Alebouyeh F, Boutron I, Ravaud P, *et al*. Psychometric properties and domains covered by patient-reported outcome measures used in trials assessing interventions for chronic pain. *J Clin Epidemiol* 2024;170:111362.
14 Frauenknecht J, Kirkham KR, Jacot-Guillarmod A, *et al*. Analgesic impact of intra-operative opioids vs. opioid-free anaesthesia: a systematic review and meta-analysis. *Anaesthesia* 2019;74:651–62.
15 Brandal D, Keller MS, Lee C, *et al*. Impact of Enhanced Recovery After Surgery and Opioid-Free Anesthesia on Opioid Prescriptions at Discharge From the Hospital: A Historical-Prospective Study. *Anesth Analg* 2017;125:1784–92.
16 Chassery C, Atthar V, Marty P, *et al*. Opioid-free versus opioid-sparing anaesthesia in ambulatory total hip arthroplasty: a randomised controlled trial. *Br J Anaesth* 2024;132:352–8.
17 Liu Y, Ma W, Zuo Y, *et al*. Opioid-free anaesthesia and postoperative quality of recovery: a systematic review and meta-analysis with trial sequential analysis. *Anaesth Crit Care Pain Med* 2025;44:101453.
18 Baumann L, Bello C, Georg FM, *et al*. Acute Pain and Development of Opioid Use Disorder: Patient Risk Factors. *Curr Pain Headache Rep* 2023;27:437–44.
19 Li X, Zhang C, Tao H, *et al*. Dexmedetomidine alleviates osteoarthritis inflammation and pain through the CB2 pathway in rats. *Int Immunopharmacol* 2023;119:110134.
20 Zhang Y, Zhou Y, Hu T, *et al*. Dexmedetomidine reduces postoperative pain and speeds recovery after bariatric surgery: a meta-analysis of randomized controlled trials. *Surg Obes Relat Dis* 2022;18:846–53.
21 Bauerschmidt A, Al-Bermani T, Ali S, *et al*. Modern Sedation and Analgesia Strategies in Neurocritical Care. *Curr Neurol Neurosci Rep* 2023;23:149–58.
22 Zhang Y, Cui F, Ma J-H, *et al*. Mini-dose esketamine-dexmedetomidine combination to supplement analgesia for patients after scoliosis correction surgery: a double-blind randomised trial. *Br J Anaesth* 2023;131:385–96.
23 Li X, Xiang P, Liang J, *et al*. Global Trends and Hotspots in Esketamine Research: A Bibliometric Analysis of Past and Estimation of Future Trends. *DDDT* 2022;Volume 16:1131–42.
24 Wang M, Xiong H-P, Sheng K, *et al*. Perioperative Administration of Pregabalin and Esketamine to Prevent Chronic Pain After Breast Cancer Surgery: A Randomized Controlled Trial. *Drug Des Devel Ther* 2023;17:1699–706.
25 Liu J, Yin J, Yin J, *et al*. Effect of esketamine-based opioid-sparing anesthesia strategy on postoperative pain and recovery quality in patients undergoing total laparoscopic hysterectomy: A randomized controlled trail. *Heliyon* 2024;10:e24941.
26 Feng C, Xu Y, Chen S, *et al*. Opioid-free anaesthesia reduces postoperative nausea and vomiting after thoracoscopic lung resection: a randomised controlled trial. *Br J Anaesth* 2024;132:267–76.
27 Santos L, Zheng H, Singhal S, *et al*. Remifentanil for tracheal intubation without neuromuscular blocking drugs in adult patients: a systematic review and meta-analysis. *Anaesthesia* 2024;79:759–69.
28 Zhang Q, Wu Y, An H, *et al*. Postoperative recovery after breast cancer surgery. *Eur J Anaesthesiol* 2023;40:552–9.
29 Hao C, Xu H, Du J, *et al*. Impact of Opioid-Free Anesthesia on Postoperative Quality of Recovery in Patients After Laparoscopic Cholecystectomy-A Randomized Controlled Trial. *Drug Des Devel Ther* 2023;17:3539–47.
30 Wang D, Liu Z, Zhang W, *et al*. Opioid-free anesthesia for quality of recovery score after surgery: A meta-analysis of randomized controlled trials. *J Clin Anesth* 2025;103:111823.
31 Léger M, Perrault T, Pessiot-Royer S, *et al*. Opioid-free Anesthesia Protocol on the Early Quality of Recovery after Major Surgery (SOFA Trial): A Randomized Clinical Trial. *Anesthesiology* 2024;140:679–89.