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Effect of perioperative dexmedetomidine on postoperative delirium in patients with brain tumours: a protocol of a randomised controlled trial

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ABSTRACT

Introduction Neurosurgery is a risk factor for postoperative delirium. Dexmedetomidine has a potential effect on reducing postoperative delirium. We aim to test the primary hypothesis that perioperative administration of dexmedetomidine reduces the incidence of postoperative delirium in patients undergoing neurosurgical resections of temporal glioma.

Methods This is a single-centre, randomised, blinded and parallel-group controlled trial. A total of 366 patients will be randomised to either dexmedetomidine group (n=183) or placebo group (n=183). Subjects assigned to dexmedetomidine group will be given a continuous infusion at 0.4 µg/kg/h after anaesthesia induction until dural closure and then immediately receive an infusion of dexmedetomidine at 0.08 µg/kg/h by intravenous analgesia pump during the first 48 hours postoperatively. Patients in the placebo group will be given comparable volumes of normal saline, and intravenous analgesia pumps contain equal amounts of sufentanil and antiemetics, but no dexmedetomidine. The primary outcome is the incidence of postoperative delirium, which will be assessed with the Confusion Assessment Method two times per day during the first five postoperative days.

Ethics and dissemination The protocol (V.1.1) has been approved by the medical ethics committee of Beijing Tiantan Hospital, Capital Medical University (KY2023-186-02). The findings of this study will be disseminated through presentations at scientific conferences and publication in peer-reviewed journals.

Trial registration number NCT06164314.

STRENGTHS AND LIMITATION OF THIS STUDY

⇒ The randomised, placebo-controlled and double-blinded trial aims to evaluate the efficacy and safety of prolonged dexmedetomidine use for preventing postoperative delirium in neurosurgical patients for temporal gliomas.
⇒ Potential challenges include the influence of dexmedetomidine on haemodynamic fluctuations, impacting effective blinding for anesthesiologists and requiring careful result interpretation.
⇒ The single-centre nature limits generalisability.
⇒ The results may contribute to evidence on perioperative dexmedetomidine use for preventing and treating delirium in temporal lobe glioma resections, optimising postoperative care and early recovery strategies.

BACKGROUND

Neurosurgical patients are susceptible to postoperative delirium, with common risk factors including advanced age, cognitive impairment, pain and longer surgery duration.[1–3] Postoperative delirium is strongly and independently associated with poor patient outcomes, but it is a challenge to prevent and treat due to its multifaceted causes and obscure pathogenesis.[4] The occurrence of delirium may be influenced by the type and the location of brain tumours,[5] with surgery for supratentorial lesions showing an association with postoperative delirium.[1]

It is reported that the incidence of postoperative delirium in patients undergoing craniotomy of frontal or temporal brain tumours is as high as 46.2%.[6] The temporal lobe, including the hippocampus and parahippocampal gyrus, plays a critical role in language function and visuospatial memory.[7] Patients with temporal tumours always present with significant neurocognitive functioning impairment prior to surgery,[8] which is associated with the risk of postoperative delirium.[9] Additionally, the incidence of postoperative delirium increased by approximately two- to three-fold in those with malignant brain tumours.[6 10] A study reported that incidence of postoperative delirium was up to 37.3% in 335 patients with glioma.[11] Furthermore, the study revealed that one of the most common lobes where tumours were centred is temporal (32%). The aggressive growth of glioma may lead to a larger tumour that might more extensively impair cortical subnetworks, which is crucial for brain connectivity that supports the cognitive reserve needed to prevent delirium.[12] Therefore, patients with temporal glioma may be at a high risk for postoperative delirium.

Dexmedetomidine is recommended for reducing the incidence and duration of the Intensive Care Unit (ICU) delirium possibly because of its analgesic properties.[13] Moreover, it may reduce the risk through its neuroprotective effects and by improving sleep disturbance[4], whereas various researches reported that dexmedetomidine improved or had little effect on delirium after noncardiac surgery.[14 15] However, our previous work demonstrated a significant benefit of dexmedetomidine in reducing delirium incidence of patients with brain tumours by more than 50%.[6]

Different dosage and timing regimens of dexmedetomidine influence the concentration of stress hormones and systemic inflammatory response to surgery.[16] A study showed that dexmedetomidine infusion (0.5 µg/kg/h) during surgery and up to 2 hours in the recovery room did not decrease postoperative delirium or affect postoperative cognition in elderly patients undergoing major elective noncardiac surgery.[15] But another study about the prolonged use of dexmedetomidine until the first postoperative morning in the same population showed that low-dose dexmedetomidine (0.1 µg/kg/h) significantly decreases the occurrence of delirium during the first 7 days after surgery.[17] This result could be attributed to the short-acting nature and loss of salutary effects following discontinuation of the infusion, which highlights the importance of timing in drug administration to prevent delirium.[15] Furthermore, although dexmedetomidine effectively reduce delirium in patients with brain tumours, there is still a 21.5% occurrence of delirium for those who received dexmedetomidine intraoperatively.[6] Continual use of dexmedetomidine during the perioperative period may be necessary to prevent the occurrence of delirium in high-risk surgical population.

Based on the prior mentioned research, we hypothesise that the intraoperative and postoperative administration of dexmedetomidine reduces the incidence of postoperative delirium in patients scheduled to undergo temporal glioma resections.

METHODS AND ANALYSIS

Study design

This is a randomised, double-blind, parallel-group and controlled trial (figure 1) and will be conducted at Beijing Tiantan Hospital, Capital Medical University. The main objective of this study is to investigate the efficacy of perioperative infusion of dexmedetomidine on the occurrence of postoperative delirium in patients undergoing craniotomy for temporal glioma. The trial has been registered on ClinicalTrials.gov on 11 December 2023 (NCT06164314). Ethical approval has been granted by the Medical Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (KY2023-186-02). Preoperative interviews will be conducted by trained research

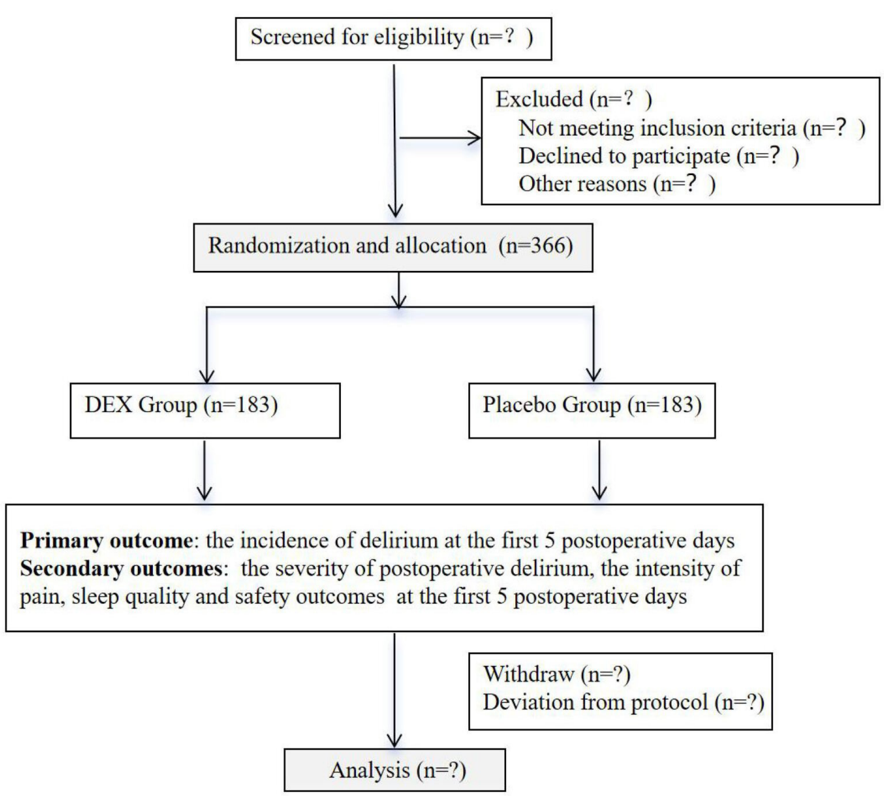

Figure 1 Recruitment flow chart. DEX, dexmedetomidine.

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assistants. Patients and their legal representatives will be informed comprehensive information about the study objectives, associated risks and benefits, and their written informed consent will be obtained. The study follows the SPIRIT. The SPIRIT flow diagram and the SPIRIT Checklist are shown in figure 1 and the online supplement file.

Patient and public involvement

Patients and/or the public are not involved in the design, conduct, reporting or dissemination plans of this trial. At the completion of the trial, a manuscript including the final results will be disseminated to all participants through their preferred method of communication indicated at the time of enrolment.

Study population

Patients with temporal glioma older than 18 years and scheduled for elective craniotomy will be screened for eligibility 1 day before surgery.

Exclusion criteria include:

1. Severe cognitive impairment before surgery (mini-mental state examination ≤20).
2. Delirium present in the 3 days prior to surgery (screened through medical and nursing records).
3. Current use of other alpha agonists (guanfacine, tizanidine, clonidine).
4. Alcohol or drugs addiction.
5. History of psychotropic medication.
6. Pregnant or lactating women.
7. History of traumatic brain injury or previous neurosurgery.
8. Allergy to dexmedetomidine.
9. History of obstructive sleep apnoea syndrome.
10. The presence of other severe medical conditions, such as severe bradycardia (heart rate below 40 beats per minute), sick sinus syndrome, second-to-third-degree atrioventricular block, as well as severe hepatic or renal dysfunction.

Randomisation and blinding

Stratified randomisation will be performed according to age <65 years or ≥65 years. Patients will be randomly assigned to either the dexmedetomidine or placebo group in a 1:1 ratio using a computer-generated random number list. The randomisation results will all be securely sealed in opaque and sequentially numbered envelopes and stored at the investigation site until the end of the study. The study drug and intravenous analgesic pump will be prepared by an independent research assistant who is not involved in the treatment or assessment. A 50-mL syringe containing dexmedetomidine (200 µg/2 mL, Jiangsu Hengrui Pharmaceuticals Co., China) solution (4 µg/mL) or an equal amount of saline 0.9% will be used for the continuous infusion during tumour resection. An intravenous analgesic pump will also be provided to responsible anaesthesiologists. All the study drugs are configured using container of the same size, colour and brand. The enrolled patients, anaesthesiologists and outcome assessors will remain blinded to the allocation until the conclusion of the study analysis. Unblinding will only be considered if there is a life-threatening situation such as cardiac arrest; the principal investigator will have access to the group allocations. In the event of unblinding, it will be reported.

Intervention and grouping

After endotracheal intubation, patients in dexmedetomidine group will receive a continuous infusion at a rate of 0.4 µg/kg/h until dural closure. Subsequently, they will be immediately provided with an intravenous analgesia pump to infuse dexmedetomidine at 0.08 µg/kg/h during the first 48 hours postoperatively. The pump regimen will be comprised of a mixture of dexmedetomidine (4 µg/kg), sufentanil (1 µg/kg), ondansetron (16 mg) and normal saline in a total volume of 100 mL. In the control group, patients will receive the identical volume of normal saline in the same setting, and intravenous analgesia pumps contain equal amounts of the analgesic and antiemetic but will not include dexmedetomidine.

Concomitant treatment

Routine monitoring will include electrocardiograph, peripheral oxygen saturation, non-invasive blood pressure, body temperature and bispectral index. After anaesthesia induction, minimal alveolar concentration of the inhalation agent, continuous invasive arterial pressure, urine output and end-tidal carbon dioxide will be additionally monitored. Bispectral index will be electronically recorded. Physiological variables will be recorded at the critical time points of operation.

General anaesthesia will be induced with midazolam, sufentanil, cisatracurium and propofol. After tracheal intubation, mechanical ventilation will be performed with a tidal volume of 6 to 8 mL/kg and a respiratory rate of 12 to 15breaths per minute to maintain the $ETCO_2$ within 35 to 40 mm Hg. Anaesthesia will be maintained with a combination of intravenous anaesthesia and sevoflurane inhalational anaesthesia. As sevoflurane will be maintained at 0.5 minimal alveolar concentration in a mixture of 40% air and 60% O2, propofol (3 to 6 mg/kg/h) and remifentanil (0.1 to 0.2 µg/kg/min) will be used to maintain bispectral index values within 40 to 60. Before head frame placement, the local infiltration anaesthesia will be performed using 0.5% ropivacaine. Sufentanil (0.1 to 0.2 µg/kg) will be injected to attenuate potent stress responses induced by noxious stimuli during skull pin fixation, scalp incision and skull drilling. During the surgery, heart rate and mean arterial pressure will be kept within ±20% of baseline. The administration of sevoflurane will cease on the replacement of the bone flap, while the infusions of propofol and remifentanil will be discontinued at the end of surgery. Patients will be extubated in the operating room after surgery and then transferred to the Post Anaesthesia Care Unit.

Subjects will receive intravenous analgesia pump during the first 48 hours postoperatively. To ensure a constant infusion rate of the experimental drug, the intravenous infusion pump will be locked and not adjusted by patients. When subjects feel pain with Numerical Rating Scale (NRS) score >3, rescue analgesics will be given.

Data collection

Specially trained research assistants will collect all perioperative data, including preoperative demographic characteristics and cognitive assessment, variables of intraoperation and postoperative complications. The primary and secondary endpoints will be assessed by the trained research assessors who are blinded to the allocation. All personal information will be kept confidential for research purposes only.

Primary outcome

The primary endpoint is the incidence of postoperative delirium. Delirium is assessed two times per day (between 08:00 and 10:00 and between 18:00 and 20:00) during the first postoperative 5 days, using three methods including the Confusion Assessment Method for Intensive Care Unit (CAM-ICU) for critical care patients[18] or the 3-min Diagnostic interview for Confusion Assessment Method (3D-CAM) for ward assessments,[19] combined with the Richmond Agitation Sedation Scale (RASS).[20]

All patients will be first assessed by RASS. If the RASS Score is ≤−4, the remaining assessment will be aborted, and the patient will be recorded as comatose. For patients with a RASS score higher than or equal to −3 admitted to the general ward, the evaluation will be conducted using 3D-CAM, which has a sensitivity of 95% and specificity of 94%.[19] For patients admitted to the ICU, the evaluation will be conducted using CAM-ICU. The CAM-ICU is a specific application for nonverbal responses from the patient to assess attention, thinking and level of consciousness.[18] It consists of four key features: acute onset of a change in mental status or a fluctuating level of consciousness, inattention, disorganised thinking and an altered level of consciousness. The patient will be diagnosed as delirium if both the first and second features are present and either the third or fourth is present. The 3D-CAM condenses the four features of delirium assessment into 20 questions, providing a convenient and comprehensive evaluation method. Before the study initiation, clinical research fellows will undergo training to conduct delirium assessments. An expert from the Department of Psychiatry will be invited to provide this specialised training.

Delirious patients will be classified into three motor subtypes: hyperactive delirium (consistently positive RASS scores +1 to +4), hypoactive delirium (consistently neutral or negative RASS score −3 to 0) and mixed delirium (altered RASS scores between positive and neutral or negative at different time points).[21] In order to obtain a more accurate estimate of the incidence of delirium, it would be assessed two times per day.[6]

Secondary outcomes

1. The severity of postoperative delirium at first 5 days after surgery: postoperative delirium severity is assessed using the Delirium Rating Scale (DRS-R-98).[22] There are three diagnostic items (0~2 or 0~3 points each) and 13 severity assessment items (0~3 points each), for a total of 46 points. The higher the score indicates a more severe level of the delirium.
2. The intensity of pain at first 5 days after surgery: the degree of surgical incision pain will be assessed at rest and on movement by the NRS,[23] ranging from 0 to 10 points, with 10 representing the worst imaginable pain. We will record maximum pain scores at different post-op time to assess peak pain experiences. For patients requiring analgesics, we will document their NRS scores before medication administration and the details of the medications used, converting dosages into morphine equivalents for final analysis.
3. Sleep quality at first 5 days after surgery: the Richards-Campbell Sleep Questionnaire will be used to assess subjective sleep quality for the postoperative 5 days.[24] The scale is composed of 5 items, including sleep depth, sleep latency, wake times, return to sleep and overall sleep quality, all of which are scored by 0~100-mm visual simulation (1 mm=1 point). The total score is the average of the five items, with a higher score indicating better sleep quality.

Exploratory outcomes

Length of ICU stay, length of hospital stays and hospital costs, other in-hospital complications and 30-day all-cause mortality.

Safety outcomes

Hypotension occurs during the start of medetomidine infusion within 48 hours after drug administration (hypotension is defined as systolic blood pressure below 95 mm Hg or below 30% of baseline), hypertension (systolic blood pressure above 180 mm Hg or 30% above baseline), bradycardia (beats per minute <40), tachycardia (beats per minute >100), delayed extubation (more than from the end of surgery to 2 hours after surgery, for the ICU patients, more than 4 hours), agitation (RASS score **>** 2 within 30 min after extubation), excessive sedation (RASS score **<** −2 within 2 hour after extubation), hypoxemia (SpO_2 <90%), and early postoperative nausea and vomiting (nausea and vomiting within 2 hours after surgery). It will be assessed from the start of medicine infusion to 48 hours postoperatively.

Data management and quality assurance

Table 1 shows data collection at each time point. Data will be collected on a case report form for each patient, and the forms with patient-identifiable information will be kept confidential. Two investigators will independently enter the data into a securely monitored electronic database with regular password updates. Access to the deidentified data sets will be limited to the study authors.

Table 1 Schedule of enrolment, interventions and assessments

	Study period							
	Enrolment	Allocation	Post-allocation					
			Postcraniotomy (day)					
Timepoint	Preoperation	Surgery day	1	2	3	4	5	30
Enrolment								
Eligibility screen	√							
Informed consent	√							
Allocation		√						
Interventions								
Dexmedetomidine group		◀────	────▶					
Control group		◀────	────▶					
Assessments								
Baseline variables		√	√	√	√	√	√	
Intraoperative data		√						
Mini-mental state examination	√						.	
Richmond Agitation Sedation Scale			√	√	√	√	√	
Confusion Assessment Method for Intensive Care Unit			√	√	√	√	√	
3-min Diagnostic interview for Confusion Assessment Method			√	√	√	√	√	
Delirium Rating Scale (DRS-R-98)			√	√	√	√	√	
Numerical Rating Pain Scale			√	√	√	√	√	
Richards-Campbell Sleep Questionnaire			√	√	√	√	√	
Adverse events			√	√	√	√	√	√
All cause death			√	√	√	√	√	√

The quality of the studies and regulatory compliance will be monitored by the Data Monitoring Committee composed of specialists in anaesthesiology, neurosurgery, ethics, statistics and methodology. The committee will audit through regular interviews or telephone calls and be responsible for terminating the research in case of severe adverse events.

After the study is completed, deidentified data sets could be shared, provided that appropriate consent and data sharing agreements are in place.

Reporting of adverse events

The adverse effect of dexmedetomidine will be closely monitored from the start to the first 5 days after the surgery. All adverse events will be documented and tracked for 30 days. The sponsor will report all serious adverse events to the medical ethics committee.

Sample size estimate and statistical analyses

An observational study reported a postoperative delirium incidence of 31% in 154 patients recovering from surgery for temporal tumours.[10] In addition, we found that the incidence of postoperative delirium after craniotomy of frontotemporal brain tumours was up to 46%.[6] Meta-analyses in non-neurosurgical patients have reported that intraoperative application of dexmedetomidine reduced the incidence of postoperative delirium by approximately 40–60%.[25 26] To avoid underpowering, we assumed a delirium incidence of 40% after temporal tumours resections and a 40% reduction with dexmedetomidine. With alpha set at a two-sided 0.05, 348 patients would provide 90% power. Accounting for about 5% loss to follow-up, we plan to enrol 366 patients with 183 in each group.

Independent statisticians who are unaware of group allocation will analyse all the data by SPSS V.23.0. Normally distributed continuous variables will be reported as the mean±SD and analysed with Student's t-tests. Non-normally distributed continuous data will be reported as median (IQR) and analysed with the Mann–Whitney U-test. Categorical data will be reported as frequency (%) and were analysed using the χ^2 test or Fisher's exact test. Time to event results will be calculated with the Kaplan–Meier estimator, with differences between groups assessed by the log-rank test.

For the primary outcome, missing data will be imputed by using the worst-case imputation scenarios.[27] Two analysis populations will be considered: the intent to treat population and the per-protocol population. The primary outcome, the incidence of postoperative delirium, will be compared between groups with a χ^2 test. Subgroup analysis will be conducted according to age (more than 65 years or not), gender, American Society of Anesthesiologists (ASA) physical status, anaesthesia duration and tumour size. Secondary outcomes will be analysed using Student's t-tests, Mann–Whitney tests or χ^2 tests as appropriate. The intention-to-treat primary outcome analysis will include all randomised subjects.

Ethics and dissemination

The study protocol was reviewed and approved by the Medical Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (IRB No. KY2023-186-02). The trial was registered at ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT06164314) on 11 December 2023. Participants are informed that their participation is voluntary and they can withdraw without penalty at any time with no impact on their care. The results of this study will be disseminated through presentations at scientific conferences and publication in scientific journals.

DISCUSSION

The development of postoperative delirium is multifactorial. Oxidative stress, neuroinflammation, circadian rhythm or melatonin dysregulation, advanced age, ASA physical status >2 and Charlson Comorbidity Index ≥2 have been shown to interact with each other and play crucial roles.[28 29] Given that advanced age could deteriorate complications such as sleep apnoea, heart failure and diabetes and that frailty and malnutrition further elevate the risk of delirium,[30 31] we have chosen to stratify by age to better control for age-related confounding factors.

It is suggested that supratentorial lesions carry a higher risk of postoperative delirium.[1] However, most studies have focused on the frontal lobe due to its role in cognition and mental activity, with little attention to the temporal lobe. In fact, the parahippocampal gyrus is also crucial for conscious awareness, largely due to its long-track transcortical connections that are vital for attention.[32] Likewise, strokes affecting the parahippocampal gyrus was associated with delirium.[33] For surgical patients, the risk of postoperative delirium may be elevated due to the disruption of the blood-brain barrier.[28] Furthermore, intracranial surgery evokes a parenchymal inflammatory reaction leading to oxidative stress, which is aggravated by impaired oxygenation of the surrounding tissue due to the formation of oedema.[34] Both of the brain pathologies and surgeries can aggravate neuroinflammation and result in higher incidence of postoperative delirium.[28] As one of the favoured sites for gliomas, it is necessary to seek a prevention of postoperative delirium.

The effects of dexmedetomidine on haemodynamic fluctuations, such as severe bradycardia and hypotension, may interfere with effective blinding of the anaesthesiologist and require careful interpretation of the results. In the present study, we omitted the loading dose of dexmedetomidine to reduce the risk of haemodynamic adverse events, considering that most of the circulatory fluctuations were related to loading infusion.[35] The efficacy and safety of dexmedetomidine administered in neurosurgical anaesthesia have already been proved in some studies.[6] The bradycardia induced by dexmedetomidine infusion might weaken the efficiency of blinding to the anaesthesiologists. However, both high intracranial pressure and intraoperative use of remifentanil could cause bradycardia. In addition, in the present study, drugs will be stored in identical containers, anaesthesiologists will not participate in postoperative assessments, and postoperative outcome assessors will not be involved in intraoperative administration, ensuring full blinding.

Timeline

The study will take approximately 2 years to complete enrolment and outcome assessment. The recruitment is anticipated to start on January 2024.

Protocol amendment

The chief investigator will be responsible for amending the protocol and making final decision. If there is any modification (eg, changes to eligibility criteria, outcomes, analyses), the principal investigator will communicate and gain approval from the China Ethics Committee of Registering Clinical Trials prior to implementation.

Dissemination

The results of this study will be disseminated through presentations at scientific conferences and publication in scientific journals.

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Contributors MiZ and MaZ drafted the protocol. JW and SL planned the statistical plans. NJ revised the draft. YP is the principal investigator, conceived the study and contributed to the study design. YP is the guarantor of this research.

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Competing interests None declared.

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

Patient consent for publication Consent obtained directly from patient(s).

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