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Preoperative walking exercise to improve prognosis in patients with supratentorial brain tumours after craniotomy: protocol for a randomised controlled trial

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ABSTRACT

Introduction Cardiopulmonary complications and cognitive impairment following craniotomy have a significantly impact on the general health of individuals with brain tumours. Observational research indicates that engaging in walking is linked to better prognosis in patient after surgery. This trial aims to explore whether walking exercise prior to craniotomy in brain tumour patients can reduce the incidence of cardiopulmonary complications and preserve patients' cognitive function.

Methods and analysis In this randomised controlled trial, 160 participants with supratentorial brain tumours aged 18–65 years, with a preoperative waiting time of more than 3–4 weeks and without conditions that would interfere with the trial such as cognitive impairment, will be randomly assigned in a ratio of 1:1 to either receive traditional treatment or additional combined with a period of 3–4 weeks of walking exercise of 10 000–15 000 steps per day. Wearable pedometer devices will be used to record step counts. The researchers will evaluate participants at enrolment, baseline, 14 days preoperatively, 3 days prior to surgery and 1 week after surgery or discharge (select which occurs first). The primary outcomes include the incidence of postoperative cardiopulmonary complications and changes in cognitive function (gauged by the Montreal Cognitive Assessment test). Secondary outcomes include the average length of hospital stay, postoperative pain, participant contentment, healthcare-associated costs and incidence of other postoperative surgery-related complications. We anticipate that short-term preoperative walking exercises will reduce the incidence of surgery-related complications in the short term after craniotomy, protect patients' cognitive function, aid patients' postoperative recovery and reduce the financial cost of treatment.

Ethics and dissemination The study protocol has been approved by Ethics Committee of Xiangya Hospital of Central South University (approval number: 202305117). The findings of the research will be shared via publications that have been reviewed by experts in the field and through presentations at conferences.

Trial registration number NCT05930288.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Setting the intervention as walking, a measure that can be precisely quantified, and considering preadmission exercise levels when allocating subjects, more precisely explores the effect of preoperative exercise on the postoperative prognosis in subjects with different physical conditions.
⇒ Because of the attribute of the intervention, it is not possible to blind subjects and researchers.
⇒ This study will be limited to the Chinese population, but we will subsequently study other populations.

INTRODUCTION

Brain tumours are widely distributed worldwide and also cause a large number of deaths.[1 2] Although craniotomy continues to be the main approach for brain tumours, it may result in complications in approximately 13%–27% of individuals, impacting their prognosis and quality of life.[3] Furthermore, the cognitive function of patients can be impacted by brain tumours, and neurological damage resulting from surgery can also decrease patients' cognitive abilities and everyday functioning. Therefore, minimising surgical complications and aiding cognitive recovery may improve the patient's prognosis and reduce healthcare costs.[4 5]

Preoperative rehabilitation, also referred to as the enhancement of a patient's preoperative physical reserve function, aims to expedite the patient's postoperative recovery by equipping them with the ability to endure surgical stress.[5] Previous studies suggest that preoperative walking may be valuable as a form of

rehabilitation. A cohort study found that walking more steps per day was associated with a reduced risk of cancer mortality.[6] Preoperative exercise, including walking, has been shown to be effective in improving patients' functional capacity after oesophagogastric cancer surgery and reducing the incidence of lung complications after lung cancer surgery.[7 8] Additionally, appropriate walking exercises can improve brain function responsible for cognition, leading to better postoperative clinical outcomes.[9]

Engaging in regular walking routines may lower the risk of cardiopulmonary issues, possibly due to enhanced aerobic exercise capacity. Walking is a valuable form of exercise for improving aerobic capacity.[10] Aerobic exercise capacity is a direct indicator of physical reserve capacity. Multiple research studies have verified that a reduction in the aerobic exercise capacity will result in a higher occurrence of cardiopulmonary complications after surgery and will negatively impact the recovery process. The 6 min walking distance is a reliable measure of the body's aerobic capacity, and an increase of 110 m is linked to a 50% decrease in the occurrence of cardiopulmonary complications following colorectal surgery.[11–13] Engaging in walking can enhance cognitive function through different neuroplasticity mechanisms, including enhanced formation of blood vessels, creation of new synapses and neurons, elevation of neurotrophic factors such as brain-derived neurotrophic factor and reduction of inflammation.[9 14 15]

Our main goal is to evaluate how a brief period of walking exercise before craniotomy in patients with brain tumours affects the occurrence of cardiovascular and pulmonary complications associated with surgery, as well as changes in cognitive function during the immediate postoperative period. The walking exercise plan will be evaluated within the framework of typical clinical pathways, which encompass improved postoperative recovery methods, and will be compared with conventional treatment.

METHODS AND ANALYSIS

Patient and public involvement

Patients and the public were not involved in the formulation of the research questions, the study design or the conduct of the study.

Study planning

This study will be implemented as a randomised controlled trial. The participants will be split into two groups: (a) an intervention group that will engage in preoperative walking exercise for a duration of 3–4 weeks alongside standard perioperative care and (b) a control group that will solely receive standard perioperative care. The study's flow of participants is illustrated in figure 1. The study will be conducted at Xiangya Hospital's Department of Neurosurgery, Central South University.

Study participants

Participant selection criteria:

Inclusion criteria

1. The participants voluntarily join this trial, sign the informed consent form and are able to comply with the research procedures.
2. Male and female outpatients or inpatients aged between 18 and 65 years.
3. Patients diagnosed with supratentorial tumours through medical history, physical examination, laboratory tests and head imaging examinations and without symptoms of intracranial hypertension or epilepsy.
4. Patients for elective surgery at low risk, as determined by medical experts based on the patient's actual condition and patient's wishes, who are initially expected to wait for more than 3–4 weeks before surgery, and for whom, it is anticipated that the condition will not progress during the waiting period.

Exclusion criteria

1. The patient with a substantial brain tumour is significantly susceptible to tumour stroke or brain herniation.
2. Patients with a clinical diagnosis of cerebral haemorrhage, intracranial infection or epilepsy.
3. Patients with acute or unstable heart disease (eg, unstable angina or severe aortic stenosis).
4. Patients with a physical status of grades 3, 4 or 5 according to the American Society of Anesthesiologists classification.[16]
5. Patients with disabling orthopaedic or neuromuscular conditions.
6. Patients with a history of clinically diagnosed cognitive impairment, such as dementia and mental retardation.
7. Patients with a current or previous diagnosis of significant mental illness, chronic neurological disease or active substance abuse (as per the Diagnostic and Statistical Manual of Mental Disorders fifth edition).[17]
8. Patients with heart failure (New York Heart Association class 3 or class 4 functional class).
9. Patients with severe chronic obstructive pulmonary disease (exertional expiratory volume in the first second of exhalation <50% of predicted value).
10. Patients with anaemia (symptomatic or haematocrit <30%).
11. Patients who have participated in other trials 1 month before or during the trial.
12. Patients who are prohibited from exercising without face-to-face supervision as assessed by the Physical Activity Readiness Questionnaire or as judged by the exercise physician based on cardiopulmonary exercise testing.[18 19]
13. Patients who are unable to cooperate during the Montreal Cognitive Assessment (MoCA) test due to impaired consciousness or mental impairment.[20]
14. Patients with motor dysfunctions, such as hemiplegia.

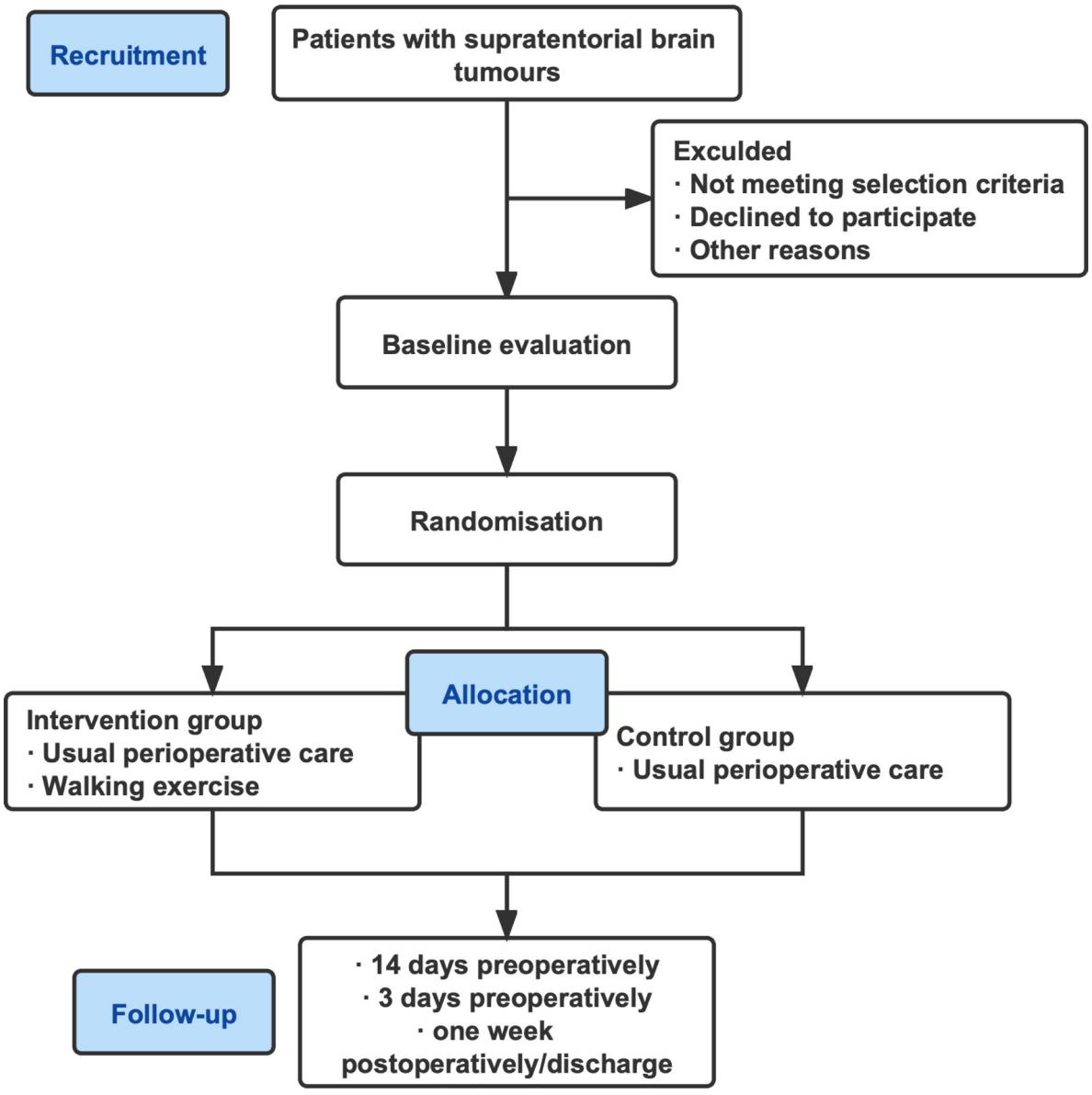

Figure 1 Study flow chart.

Recruitment and selection

Our trial will recruit 160 patients. Recruitment of participants will take place at Xiangya Hospital's Department of Neurosurgery from 1 March 2024 to 1 April 2026. The neurosurgery research team at Xiangya Hospital will identify participants through eligibility screening conducted during preoperative clinics.

Randomisation, assignment, concealment and masking

After the initial evaluation and enrolment, participants will be assigned randomly to either the intervention or control group in a 1:1 ratio. To achieve a balanced distribution, we will use minimal allocation methods considering factors such as tumour type (glioma or meningioma, preliminary judgement by professional doctors through imaging examinations and other means), age group (18–39 years, 40–59 years and ≥60 years), gender (male or female) and preadmission exercise level (exercise level within 6 months ≤3.5 marginal metabolic equivalent task hours per week (mMET-hours/week), >3.5 mMET-hours/week and ≤8.75 mMET-hours/week, >8.75 mMET-hours/week and ≤17.5 mMET-hours/week, >17.5 mMET-hours/week[21]). The measurement of physical activity level will use mMET-hours/week.[22] Subjects' weekly duration of physical activity will be calculated based on the frequency of physical activity and the duration of each session. The mMET hours/week will be calculated from the weekly duration of physical activity versus the intensity of the activity.[22 23] If the level of physical activity is not clearly stated, we will classify the mentioned activity as either light, moderate or vigorous based on the provided description, using the Physical Activity Compendium as a reference.[24] For light activity, an mMET value of 1.5 will be assigned, while moderate activity will have an mMET value of 3.5, and vigorous activity will be assigned an mMET value of

7.0.[25] The allocation order will be computer generated and accessed by researchers independent of the recruitment process, protocol development, trial intervention and outcome assessment. Sealed envelopes will be created in accordance with the recruitment order to conceal the allocation order and treatment assignment. The evaluation will be conducted by evaluators who have no knowledge of the assignment of treatments. Researchers and participants cannot remain unaware of the intervention or control groups due to the inherent nature of the intervention.

Intervention

During the trial, professional kinesiologists will conduct a comprehensive demonstration of the training programme, offering feedback and making corrections based on the participant's performance. The target physical activity level for participants is to walk 10 000 steps per day, meeting or exceeding this level (but not exceeding 15 000 steps) 7 days a week for 3–4 weeks. Participants will be advised to gradually increase their daily step count in proportion to their physical condition. The exercises will include brisk walking or jogging, using the indoor treadmill equipped by the Neurosurgery Department of Xiangya Hospital or outdoors. Every exercise session will start with a 5 min warm-up and conclude with a 5 min cool-down. The researcher will provide the subjects with free wearable pedometer devices made by Samsung (Samsung Gear S3) to measure the subjects' daily step count, which has been found to provide more precise measurements.[26] Every participant will be provided with regular perioperative care and postoperative follow-up at the Xiangya Neurosurgery Outpatient Centre, overseen by physicians who are not part of this research. We will terminate the intervention early when the subject's physical condition deteriorates to such an extent that walking exercise cannot be supported or when the subject requests to stop exercising.

Measures

The initial evaluation will occur at the following time intervals: enrolment, baseline (T0), 14 days prior to surgery (T1), 3 days before surgery (T2) and 1 week after surgery/discharge (T3, select whichever occurs first). Table 1 outlines the key time points for the assessments. Patient interviews will gather information about sociodemographics, while medical records will provide data on medical history, cancer diagnosis, treatment and more.

Outcomes

Primary outcomes

1. Incidence of postoperative cardiopulmonary complications (pneumonia, thrombosis, etc (by Japan Clinical Oncology Group postoperative complications criteria[27])).

Table 1 Overview of assessments in the study

Period	Enrolment	Baseline (T0)	14 days preoperatively (T1)	Three days preoperatively (T2)	1-week postoperatively/ discharge (T3, select whichever occurs first)
Screening for eligibility	X				
Written informed consent	X				
Inclusion/exclusion criteria	X				
Basic information (demographic data, medical history, cancer diagnosis, etc)	X	X			
General examination (blood pressure, heart rate, height, etc)	X	X			
Respiratory complications (pneumonia, pulmonary embolism, etc)					X
Cardiovascular complications (hypertension, thrombosis, etc)					X
Cognitive function (by MoCA, MoCA Chinese 7.1 for T0/T1 and MoCA Chinese 7.2 for T2/T3)		X	X	X	X
Pain (by 0–10 Numerical Rating Scale)					X
Satisfaction (by Patient Satisfaction Questionnaire-III)					X
Preadmission exercise level		X			
Cerebral haemorrhage					X
Intracranial infections					X

MoCA, Montreal Cognitive Assessment.

2. Cognitive function change (by MoCA, MoCA Chinese 7.1 (0–30 points, with higher scores generally indicating better cognitive function) for T0/T1 and MoCA Chinese 7.2 (0–30 points, with higher scores generally indicating better cognitive function) for T2/T3).

Secondary outcomes

1. Average length of stay (up to 12 weeks).
2. Postoperative pain (by 0–10 Numerical Rating Scale (0–10 points, with higher scores generally indicating more severe pain)).
3. Subject satisfaction (by Patient Satisfaction Questionnaire-III (50–250 points, with higher scores generally indicating higher satisfaction)).
4. Cost of care.
5. Incidence of other postoperative surgery-related complications (cerebral haemorrhage, intracranial infections, etc).

The length of stay will be recorded by the researcher at the time the subject is discharged from the hospital. The researcher will estimate the costs of hospitalisation and interventions based on data from hospital records, with unit costs taken from standard estimated costs from the Office of Medical Pricing. The analysis of programme implementation costs will take into account clinician salaries, overheads and equipment costs. Formal care costs will be extracted from medical records and institutional databases, considering preoperative characteristics, type of surgery and postoperative recovery, and any complications.

Adherence

Subject adherence will be measured by the subject's compliance with the preoperative prescribed exercise regimen.

$$Adherence = \frac{Actual\ steps\ of\ preoperative\ walking\ exercise}{Steps\ of\ walking\ exercise\ required\ before\ surgery}$$

Throughout the trial, healthcare professionals and exercise specialists will emphasise to subjects and their companions the importance of subjects carrying the wearable pedometer with them, encouraging subjects to exercise and tracking their use regularly. Clinicians will monitor subjects and follow-up with them on a daily basis. If a subject is found not to have worn a pedometer the previous day or if the pedometer recorded fewer than 10 000 steps the previous day, the subject will be contacted to understand the reason for this and measures will be taken to ensure adherence. Poor adherence will be indicated if the subject is ≤80% adherent or ≥120% adherent. If subjects are not adhering well, the reason for this should be identified and documented.

Safety

Before conducting baseline testing, all participants will be required to undergo medical screening to verify their eligibility for participation. The researcher will follow the subjects according to the planned process, perform examinations and record the results. If there are abnormal values on the tests that are difficult to interpret, the investigator will repeat them until the values return to normal or are accurately interpreted. If the participant's condition progresses or any other adverse events are detected during the trial, the investigators will immediately remove the participant from the study and apply appropriate treatment measures. Assessment for adverse events will include classification, grade, relationship to the intervention, management measures and outcome. When there is an early withdrawal, the investigator will exert maximum effort to ascertain the cause of withdrawal, precisely document the withdrawal time from the trial and conduct all necessary tests for the final follow-up.

Statistical analysis

Sample size

Sample size was calculated by using PASS 2023 software. Considering cognitive function, according to initial predictions, the disparity in MoCA scores between the two groups by the conclusion of the monitoring period was 4, with an approximate SD of 7 for their overall score. To achieve a power of 80% with a two-sided type I error rate (alpha) set at 2.5%, it is necessary to have a sample size of 128 subjects. Considering a 20% drop-out rate, 160 subjects will need to be enrolled to ensure that 128 subjects complete the trial. Considering cardiovascular complications, according to initial predictions, the incidence of cardiopulmonary complications in the intervention group is about 0.1, and in the control group, it is about 0.35. To achieve a power of 80% with a two-sided type I error rate (alpha) set at 2.5%, it is necessary to have a sample size of 98 subjects. Considering a 20% drop-out rate, 124 subjects will need to be enrolled to ensure that 98 subjects complete the trial. Considering respiratory complications, according to initial predictions, the incidence of cardiopulmonary complications in the intervention group is about 0.05, and in the control group, it is about 0.25. To achieve a power of 80% with a two-sided type I error rate (alpha) set at 2.5%, it is necessary to have a sample size of 112 subjects. Considering a 20% drop-out rate, 140 subjects will need to be enrolled to ensure that 112 subjects complete the trial. Since the required sample size calculated based on cognitive function scores is larger, to ensure the reliability of the results, this sample size will be used as the final sample size. It is anticipated that 160 patients will be recruited to complete the trial.

Statistical analyses

Data analysis will be carried out by professional statisticians using SPSS (Statistics 29) software. The baseline characteristics of each arm will be compared. We will provide summary statistics for continuous variables, including means, SD, medians and ranges as necessary, as well as for categorical variables, including counts and proportions. To compare the distributions of each response variable and patient characteristics between the arms, various graphical methods, such as boxplots, case profile plots and labelled scattered plots, will be employed. A

linear mixed model will be used to simulate the longitudinal variation in the main responses between groups. By employing a hybrid approach, the covariance of patients is taken into consideration, enabling the accomplishment of the following tasks: (1) assessing changes in patterns over time by analysing the interplay between the intervention group and duration and (2) detecting and confirming disparities between groups at particular time intervals using linear contrasts. Our main analyses will include both unadjusted and adjusted versions, where adjustments will be made for baseline factors including gender, age, disease stage and baseline outcome.

Data management

All data will be accurately and completely recorded on the case report form after data collection. Two assessors will each independently check to ensure the accuracy of the data. The Ethics Committee of Central South University's Xiangya Hospital will be in charge of monitoring the data. The committee will supervise the entire project, track the progress, provide guidance on scientific validity and ensure the project's execution. The committee will receive annual reports from the research team.

ETHICS AND DISSEMINATION

Approval for the study was obtained from the Ethics Committee of Xiangya Hospital of Central South University, ensuring adherence to ethical standards. All modifications to the protocol that could impact the implementation of the study will be presented to the ethics committee for approval (unique protocol ID 202305117). The research will be carried out in compliance with the Declaration of Helsinki. The study is registered with ClinicalTrials.gov (NCT05930288, The Effect of Preoperative Walking Exercises on the Prognosis of Supratentorial Brain Tumours Patients After Craniotomy).

At the time of subject recruitment, researchers will notify potentially qualified participants about the specifics of the research. Ample time will be provided to patients for asking questions and making decisions. Informed consent will be obtained from eligible patients who choose to participate in the trial at the clinical research facility. The care and treatment received by patients who choose not to participate will not be compromised in any way.

The findings of the research will be shared via publications that have been reviewed by experts in the field and through presentations at conferences. On the conclusion of the study, the findings will be shared with the participants and their families. To protect patient privacy, individual patient data (IPD) will not be disclosed. Other researchers who wish to access IPD may contact the corresponding author to make a request. If the request is approved by the ethics committee, the corresponding author may share IPD.

DISCUSSION

Previous studies have indicated that preoperative walking exercise can reduce postoperative complications in a safe, convenient and more cost-effective way. The purpose of this research is to investigate whether a brief precraniotomy exercise regimen for people with supratentorial brain tumours can reduce the occurrence of heart and lung problems, protect cognitive abilities and offer insights into the impact of preoperative walking on pain after surgery, patient satisfaction during hospital stay and healthcare costs. The preliminary findings may indicate if precraniotomy walking leads to improved postoperative outcomes, and stratified results can help investigate the impact of preoperative exercise on postoperative recovery at a more specific level and aid in the development of specific protocols.

Research has indicated that the level of motivation has a substantial impact on the physical activity patterns of individuals diagnosed with cancer.[28] If a randomised controlled trial demonstrates the advantages of a preoperative walking regimen for patients with brain tumours who need craniotomy, it would motivate patients to participate in physical activity and offer the necessary evidence to endorse patients' involvement in a carefully tailored and individualised physical exercise programme. In conclusion, the study's findings will guide current perioperative practice and provide future research directions.

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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.

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