The effects of protective lung ventilation on regional cerebral oxygen saturation in intracranial tumor operative during dura opening：study protocol for a randomized controlled trial

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Study protocol

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Abstract

Objective:To investigate the effects of protective lung ventilation on regional cerebral oxygen saturation during dura opening, that is from after dura opening (T1a) to before dura closing (T2b), in patients undergoing intracranial tumor surgery.

Methods: This is a randomized, controlled trial which will be carried out at the second affiliated hospital of Soochow University. Fifty-four patients undergoing intracranial tumor surgery will be randomly allocated to the control group and the protective lung ventilation group. In the control group, tidal volume (VT) will be set at 8 ml/kg of ideal body weight, but positive end-expiratory pressure (PEEP) and recruitment maneuvers will not be used. In the protective lung ventilation group, VT will be set at 6 ml/kg of ideal body weight combined with individualized PEEP (PEEPx) during intraoperative dura mater opening, but in other periods of general anesthesia, VT will be set at 8 ml/kg of ideal body weight. Titration method of individualized PEEP (PEEPx) [1]: VT and respiratory rate will be fixed at 6ml/kg and 15 beats per minute during PEEP trial. Titration can only begin once the dura is opened. The titration for the individual PEEP can then be initiated by increasing PEEP from 2 to 10cm H2O incrementally. Each PEEP level (2, 3, 4, 5, 6, 7, 8, 9, 10cm H2O) will be maintained for 1 minute, and the pulmonary compliance of the last cycle will be recorded at each PEEP level. At last, the PEEP value at the highest compliance will be selected as the individual PEEP of patient. Regional cerebral oxygen saturation (rSO2), partial pressure of oxygen and carbon dioxide, oxygenation index, lactic acid level in arterial blood, and mean arterial pressure will be compared before anesthesia (T0), before dura opening (T1), after dura closing (T2) and 24 h after surgery (T3). Pulmonary ultrasound scores will be performed at T0 and T3.The degree of brain relaxation before and after protective lung ventilation will be evaluated by the surgeon using the brain relaxation scale. Amount of vasoactive drugs used and blood loss will be recorded during intraoperative dura mater opening. The total duration and secondary rate of surgery also will be recorded. Discussion: This study aims to determine whether intraoperative pulmonary protection strategy can improve regional cerebral oxygen saturation in patients undergoing intracranial tumor surgery, and to investigate whether intraoperative pulmonary protection strategy does not affect the degree of brain tissue swelling and the amount of blood loss during surgery. If our results are positive, this study will show that intraoperative pulmonary protection strategy can be used effectively and safely in neurosurgical patients undergoing craniotomy for tumor resection.

Trial registration: chictr.org.cn, ID: ChiCTR1900025632. Registered on 3 September 2019. tudy protocol version 1.0.

Background

With the development of society and the progress of science and technology, more and more people receive delicate and complex procedures such as neurosurgery. Almost all these patients are under general anesthesia which is basically inseparable from mechanical ventilation. 15%-20% of patients had different degrees of alveolar collapse at the bottom of the lung before operation, and this phenomenon

could persist for several days after operation due to the influence of mechanical ventilation of endotracheal intubation. The pulmonary complications play an important role in death and disability in patients with general anesthesia[2-4].Craniotomy takes a long time, and prolonged mechanical ventilation leads to a higher risk of postoperative atelectasis and pulmonary infection[5,6]. Atelectasis and pulmonary infection can seriously affect pulmonary ventilation, even lead to severe hypoxemia. Moreover, the long period of brain operation is more likely to cause the imbalance of brain oxygen supply and consumption. The change of brain oxygen supply and consumption balance may lead to the change of brain function, and the change of postoperative cognitive function[7]. POCD will lower the quality of life, increase mortality and aggravate the financial and mental burden of patients.

Protective lung ventilation (PLV) strategies have been recognized by many anesthesiologists and widely used in clinical anesthesia [8,9].Relevant studies suggest that low-tide volume combined with PEEP ventilation and alveolar recruitment maneuver (ARM) is the most widely used lung protective ventilation strategy, which can reduce lung volume damage and pulmonary barotrauma , improve pulmonary function and decrease postoperative pulmonary complications[10].Theoretically, low tide volume prevents excessive alveolar expansion [11] and higher PEEP prevents pulmonary atelectasis [12]. However, traditional protective lung ventilation strategies often need to gradually increase PEEP to the level of 20 cm H2O or even higher [6,10], which will obviously affect the circulation and intracranial pressure of patients [13], and may increase airway pressure, reduce cerebral venous reflux and intraoperative operating space, thus limiting its application in patients with craniotomy. In addition, in clinical work, anesthesiologists often use a single PEEP or pulmonary retention mode, ignoring individual differences among patients, thus affecting the effect of protective lung ventilation [1,14,15].

In recent years, with the development of medical monitoring equipment, regional cerebral oxygen saturation monitoring technology [16,17] has been gradually developed and used in clinical anesthesia. It provides a condition for real-time monitoring the perfusion level of brain tissue in patients undergoing craniotomy, and provides technical support for carrying out clinical research on protective pulmonary ventilation during craniotomy.

Near infrared spectrometer (NIRS) using near infrared technology is similar to the pulse oxygen monitor which is commonly used. Near-infrared light with wavelength of 650~1100nm has a good penetrability to human tissues such as scalp, skull and brain, even up to several centimeters. The oxygenation of brain tissues was evaluated by measuring the changes in the absorption spectrum, which was accompanied with changes in oxygenation state , of the major color base (Hb) attenuated in the intracranial area of NIR light result in the changes in the light intensity of penetrating organisms [18].

There are no large randomized controlled trials to study the efficacy and safety of intraoperative pulmonary protective ventilation strategies in patients undergoing craniotomy, because of there are risks associated with PEEP and recruitment maneuvers. Due to the disappearance of intracranial pressure after the dura opening during craniotomy, individualized protective pulmonary ventilation strategy may avoid the adverse effects on cerebral perfusion, but there is no research on this. However, with the increasing

number and complexity of neurosurgery, it is necessary to adopt appropriate protective ventilation strategies during anesthesia. The purpose of this study was to evaluate the effects of protective lung ventilation strategies during dura opening and conventional ventilation on regional cerebral oxygen saturation in patients undergoing intracranial tumor surgery.

Methods

Study design

This is a single-center, randomized, parallel-group controlled trial which is being conducted at the second affiliated hospital of Soochow University. Recruitment began in November 2018. Schedule of enrolment, interventions, and assessments will be shown in figure 1. Basic information of patients will be shown in table 1.

Randomization will be conducted via a computergenerated randomized controlled table. Patients who meet the enrollment criteria will be randomly allocated to the two groups within 24 h before surgery. The allocation ratio is 1:1. Permuted randomization will be used and stratified by age. The designated staff will perform the allocation sequence. The designated staff assistants will assign participants to interventions. This research staff will implement the allocation sequence through sealed, opaque and stapled envelopes. Corresponding envelopes will not be opened until the enrolled participants complete the trial. The anesthesiologist who is responsible for the anesthesia implementation will know the grouping but not participate in the follow-up visit. However, the neurosurgeon who evaluates brain relaxation will be blinded to the group allocation. The patients and the outcome assessor are all blinded to the grouping.

Tab 1. Patient Characteristics and Baseline Data

Characteristic	C Group	P Group
Male/female		
Age, yr		
BMI, kg/m2		
IBW, kg		
ASA physical status, I/II		

Selection and withdrawal of participants

Recruitment

Participants will be recruited from the neurosurgical wards and identified by their presence on surgical lists. The investigator informs the participant or the participant’s legal representative of all aspects. The study intervention will be completed immediately after the surgery, but follow-up visits will extend to 1 week after surgery. The medical records will be reviewed following hospital discharge for inhospital complications and medication usage.

Inclusion criteria

1.Patients scheduled to receive elective intracranial primary intra-axial tumor resection who are younger than 65 years and elder than 18 years

2. The maximum diameter of the tumor is 2~5 cm
3. ASA class for □-□
4. 18.5□BMI□28
5. Glasgow Coma Scale score of more than 8 points

Exclusion criteria

1. Patients with chronic lung disease□pulmonary infection and other severe pulmonary complications such as acute respiratory failure
2. Patients with a history of pulmonary surgery
3. Patients with severe brain, heart, liver and kidney diseases
4. Patients with nerve injury affecting breathing preoperative
5. Pregnant women
6. Refuse to participate in the researcher

Termination criteria

1. Duration of anesthesia <4 h or >8 h
2. Patients with significantly increased intraoperative intracranial pressure or swelling of brain tissue

3. Patients with intraoperative endotracheal catheter after surgery
4. Repeat intubation or operation within 24 h after operation

Study intervention

Related parameter setting during operation

All patients will be randomly allocated to the control group (C group) and the pulmonary protective ventilation group (P group) according to the computer-generated random number table. In the control group, VT will be set at 8 ml/kg of ideal body weight, with PEEP = 0, and the recruitment maneuver will not be used. In the protective lung ventilation group, VT will be set at 6 ml/kg of ideal body weight combined with individualized PEEP (PEEPx) during intraoperative dura mater opening[6,7], but in other periods of general anesthesia, VT will be set at 8 ml/kg of ideal body weight. The ideal body weight of male patients is calculated as (centimeters of height–80) ×0.7 and of female patients is calculated as (centimeters of height–70) ×0.6.

PEEP may cause swelling of the brain and increase the risk of coughing during neurosurgery. To avoid coughing before using PEEP, sufficient anesthesia depth or adequate muscle relaxation will need to be acheived.. All patients will be given volumetric controlled mechanical ventilation, and the inhalation oxygen fraction (FiO2) will be set at 0.5, I:E = 1:2. The respiration rate will be adjusted according to the result of end-expiratory CO2, and the end-expiratory CO2 will be maintained between 30-35 mmHg.

Peripheral venous access will be established after the patient enters the operating room. If necessary, central venous access will be established. Noninvasive blood pressure, electrocardiogram, heart rate, SpO2 and BIS will be routinely monitored. Radial artery catheterization under local anesthesia will be used to monitor invasive arterial pressure and collect blood samples. All of the above data will be collected completely. Induction will be started after oxygen flow of 0.1 L/kg/min was given by mask for 2 min: fentanyl 5ug/kg, etomidate 0.3mg /kg, rocuronium 0.6mg/kg, endotracheal catheter will be inserted to confirm the correct position of catheter, and volume controlled mechanical ventilation will be conducted by primus anesthesia machine (Drager, Germany).The VT will be set 8 ml/kg of ideal body weight, the inhalation-expiration ratio (I: E)= 1:2, the oxygen flow is 1 L/min, and the respiratory rate will be adjusted to maintain PetCO2 at 30~35 mmHg. 1% sevoflurane combined with propofol and remifentanil to maintain anesthesia, and BIS value will be maintained at 45~55. During the process, intermittent injection of fentanyl and rocuronium to deepened anesthesia. Extubation indications: patients were awake and cooperated, and muscle relaxation monitoring TOF>90%.[19] Intraoperative fluid intake and urine volume will be monitored closely. Regional cerebral oxygen saturation (rSO2)

will be recorded in the tumor surgery area of the patients anesthesia (T0), 30 min after intubation (T1), before extubation (T2), 30min after extubation (T3), 24 h after surgery (T4) and 72 h after surgery (T5). Arterial blood of the patients was collected for blood gas analysis to obtain oxygenation index and lactic acid level.

Study objective

Primary outcome

The primary outcome of this study is to investigate whether the pulmonary protective ventilation significantly improve the regional cerebral oxygen saturation (rSO2) in patients.

The secondary outcomes are as follows:

1.Changes between preoperative and postoperative in pulmonary ultrasound in patients who use the pulmonary protective ventilation. Lung ultrasound score based on a comprehensive 12 area per lung investigation will be used to evaluate postoperative atelectasis: the lowest score is 0, that is no atelectasis occurred, and the highest score is 36.

2.Whether the mean arterial pressure changes significantly during intraoperative pulmonary protective ventilation.

3.Whether the partial pressure of oxygen and carbon dioxide, oxygenation index, lactic acid level in arterial blood changes significantly during intraoperative pulmonary protective ventilation.

4.Whether the amount of vasoactive drugs and blood loss will be significantly changed during the pulmonary protective ventilation.

5.Intraoperative brain relaxation. Brain relaxation will be scored by the neurosurgeon after opening the cranium and before opening the dura. They will use a 4-point scale: 1, completely relaxed; 2, satisfactorily relaxed; 3, firm brain; 4, bulging brain

6.The secondary operation rate in one week after surgery.

Tab 2.Intraoperative global parameters

	C Group	P Group
Tidal volume, ml		
Individual PEEP，cmH2O		
Duration of anesthesia, min		
Tumor size (maximum diameter)		
Tumor depth (maximum distance from brain surface)		
Brain relaxation scale(T1)		
Brain relaxation scale(T2)		
Pulmonary ultrasound score(T0)		
Pulmonary ultrasound score(T3)		
Reoperation rates		

Tab 3.Parameters during dura opening

	C Group	P Group
Duration of dura opening		
The amount of bleeding，ml		
Dosage of vasoactive agent，mg		

Tab 4-1 Comparison of rSO2

	T0	T1	T2	T3
C Group				
P Group				

Tab 4-2 Comparison of partial pressure of oxygen

	T0	T1	T2	T3
C Group				
P Group				

Tab 4-3 Comparison of Partial pressure of carbon dioxide

	T0	T1	T2	T3
C Group				
P Group				

Tab 4-4 Comparison of Oxygenation index

	T0	T1	T2	T3
C Group				
P Group				

Tab 4-5 Comparison of lactic acid

	T0	T1	T2	T3
C Group				
P Group				

Tab 4-6 Comparison of mean arterial pressure

	T0	T1	T2	T3
C Group				
P Group				

T0:Before anesthesia；T1: Before dura opening；T2:After dura closing；

T3:24h after surgery；

Reporting of adverse events

All adverse events will be recorded and closely monitored until resolution or stabilization. In the event of any serious adverse event, it will be immediately reported to the Endpoint

Adjudication Committee, which will determine the severity and causality of the adverse events. The chief investigator will be responsible for all adverse event reporting.

Withdrawal from the trial

We will consider patient withdrawal from the trial if the following conditions occur: (1) severe brain swelling during the operation; (2) the patient has a cough during surgery; (3) the patient has persistent hypotension and circulatory instability.

Data collect and management

All the patient information will be obtained through the electronic medical record system. The consent of the treating neurosurgeon, who will help us make the neurological diagnosis, has also been obtained. All personal information will be collected through the hospitalized medical records by a member of the research team and be kept strictly confidential for research purposes only. The research team members will be responsible for maintaining personal data. Only the primary investigator and the designated researcher can obtain interim results and final test data.

Data Monitoring Committee (DMC)

The project will be monitored by a Data Monitoring Committee (DMC) composed of specialists in anesthesiology, ethics, statistics and methodology. The DMC will audit through regular interviews or telephone calls.

Sample size and justification

We calculated the sample size through the website http://www.sample-size.net/sample-size-proportions/.

The difference of brain oxygen saturation before and after surgery was 3.6 ± 4.1, $\alpha = 0.05$, $\beta = 0.2$[7]. Based on this, it can be calculated that the sample size required for our study is 44 cases, plus 20% shedding rate, a total of 53 cases (44+44*20%) need to be recruited. Due to the 1:1 distribution ratio, a total of 54 cases were recruited.

Statistics

The SPSS 19.0 software package for Windows (SPSS, Inc., Chicago, IL, USA) will be used for all statistical analyses. The regional cerebral oxygen saturation, arterial oxygenation

index and lactic acid level will be analyzed by using the chi-square test ($\chi 2$). Brain relaxation will use the Mann-Whitney U test for analysis. The incidence of reoperation rate will be expressed as the number of patients (percentage), and analyzed by using the chi-square ($\chi 2$). After the follow-up of half of the cases, the interim analysis will be conducted to evaluate the validity of the main results.

Discussion

This study is a single-center, randomized, parallel-controlled trial of exploring whether protective lung ventilation during intraoperative dura opening can significantly improve regional cerebral oxygen saturation in neurosurgical patients.

The incidence of postoperative pulmonary complications (PPCs) is high due to the long mechanical ventilation in neurosurgery. Qaseem et al. [20] reported that the risk of PPCs increased when operation time is more than 4 h. The incidence of PPCs was 28.4% (20.2–37.9%) in patients with neurosurgery lasting for longer than 300 min [21]. PEEP can lower the incidence of postoperative respiratory complications, prevent atelectasis and reduce the risk of VILI.

In this study, individual PEEP (< 10cmH2O) will use to avoid the effect of high PEEP on intracranial pressure (ICP).PEEP can be safely used in craniotomy is a crucial issue. Therefore, pulmonary protective ventilation will be performed during dura opening and cerebral relaxation will be assessed before dura incision. If the intracranial pressure is elevated enough to affect the operation for using PEEP, we will abandon the case and change ventilation parameters. The case will be reported to the principal investigator.

Regional cerebral oxygen saturation (rSO2) is actually the mixed oxygen saturation of local brain tissues, which can better reflect the change of brain oxygen supply and consumption balance during perioperative period. Samra et al. [22] studied 100 patients who underwent carotid endarterectomy, then found that if the rSO2 value decreased by 20% compared with the baseline value after internal carotid artery occlusion, it predicted the possibility of neurological complications, and indicated that its sensitivity was 80% and specificity was 82%. Since the ratio of cerebral blood volume to arterial/venous blood flow is approximately 20:80, NIRS mainly represents cerebral venous oxygen saturation, which is completely unaffected by hypoxemia and hypocarbonemia, and better reflects the changes in the balance of oxygen supply and consumption in the brain [23]. Near infrared spectroscopy (NIRS) as a brain oxygen monitoring method has following characters: continuous and noninvasive, convenient, high degree of sensitivity and specificity. Monitoring regional cerebral oxygen saturation can detect changes of the cerebral blood flow and oxygen supply and consumption balance in the brain area as early as possible, and judge the degree of cerebral ischemia and hypoxia and the changes of brain function.

Timely adjustment of anesthesia plan is helpful to guide perioperative anesthesia management, so as to prevent POCD, shorten hospitalization period and improve quality of life.

We focus on whether pulmonary protective ventilation strategy can affect cerebral venous reflux and brain tissue oxygenation, and ultimately, the prognosis of patients. Protective lung ventilation after incision of dura can reduce the returned blood volume that results in exposing potential bleeding spots, which is beneficial for the surgeon to stop bleeding. Due to the opening dura, the intracranial pressure disappeared, and the decreased cerebral perfusion pressure caused by the expansion of the lung would be improved.

The study is a prospective, randomized controlled trial. This study aims to investigate the effect of intraoperative pulmonary protective ventilation in neurosurgical craniotomy. If we can demonstrate that intraoperative pulmonary protective ventilation can safely and effectively improve brain oxygen saturation in patients, it will improve the prognosis of neurosurgical patients and reduce medical costs.

Trial Status

The study was also registered on the registry website http:// chictr.org.cn/ with the registration number ChiCTR1900025632 on 3 September 2019. Protocol version 1.0, 3/9/2019. The study began on 3 September 2019, and the planned completion date will be September 2020. Trial status was currently recruiting. The recruitment began on 3 September 2019, and the planned completion date will be June 2020.

Abbreviations

VT : tidal volume

PEEP : positive end-expiratory pressure

rSO2: regional cerebral oxygen saturation

PLV: protective lung ventilation

ARM: alveolar recruitment maneuver

NIRS: near infrared spectrometer

FiO2: oxygen fraction

PPCs: postoperative pulmonary complications

ICP: intracranial pressure

Declarations

Ethics approval and consent to participate

Ethics Committee of the Second Affiliated Hospital of Soochow University approved the study on 23.11.2018 (File number EC-AF(JD)-06/6.1, study protocol version 1.0). The study is designed in accordance to the principles of the Declaration of Helsinki. Written informed consent was obtained from every enrolled patient upon request by the review board.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no competing non-financial/financial interests.

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This study was not funded.

Authors' contributions

Hairui Liu conceived and designed the

study, coordinates the overall study, and contributed to the final manuscript. Jinlu Li conceived and designed the study, coordinates the overall study, and contributed to the final manuscript. Xuemei Wu participated in the design of the study and drafted the manuscript. Ying Huang and Yueqin Liu performed the sample size calculation, drafted the statistical analysis plan. Hong Xie participated in the design of the study. Jun Dong conceived the study, and guided the calculation of the sample size and the plans of the statistical analysis. All authors read and approved the final manuscript.

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Authors’ information

Not applicable.

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