BMJ Open Efficacy and safety of remifentanil dose titration to correct the spontaneous hyperventilation in aneurysmal subarachnoid haemorrhage: protocol and statistical analysis for a prospective physiological study

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ABSTRACT

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Introduction Spontaneous hyperventilation (SHV) is common in aneurysmal subarachnoid haemorrhage (aSAH). The reduction in arterial partial pressure of carbon dioxide (PaCO₂) may change the brain physiology, such as haemodynamics, oxygenation, metabolism and may lead to secondary brain injury. However, how to correct SHV safely and effectively in patients with aSAH has not been well investigated. The aim of this study is to investigate the efficacy and safety of remifentanil dose titration to correct hyperventilation in aSAH, as well as the effect of changes in PaCO, on cerebral blood flow (CBF).

Methods and analysis This study is a prospective, single-centre, physiological study in patients with aSAH. The patients who were mechanically ventilated and who meet with SHV (tachypnoea combined with PaCO₂ <35 mm Hq and pH >7.45) will be enrolled. The remifentanil will be titrated to correct the SHV. The predetermined initial dose of remifentanil is 0.02 µg/kg/min and will be maintained for 30 min, and PaCO, and CBF will be measured. After that, the dose of remifentanil will be sequentially increased to 0.04, 0.06, and 0.08 µg/kg/min, and the measurements for PaCO, and CBF will be repeated 30 min after each dose adjustment and will be compared with their baseline values.

Ethics and dissemination This study has been approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University (KY 2021-006-02) and has been registered at ClinicalTrials.gov. The results of this study will be disseminated through peer-reviewed publications and conference presentations. Trial registration number NCT04940273.

INTRODUCTION

(SHV) Spontaneous hyperventilation is common in patients with aneurysmal subarachnoid (aSAH). haemorrhage Previous studies have shown that SHV can occur in 55%-83% of patients with aSAH and is associated with an increased risk of delayed

STRENGTHS AND LIMITATIONS OF THIS STUDY

- \Rightarrow To the best of our knowledge, this is the first study to evaluate the efficacy and safety of remifentanil for the correction of spontaneous hyperventilation in aneurysmal subarachnoid haemorrhage.
- \Rightarrow The study is designed as a single-centre, prospective, exploratory study with relatively small sample size.
- \Rightarrow We chose 30 min as observation time for changes in arterial partial pressure of carbon dioxide and cerebral blood flow following remifentanil adjustment, the changes after the trial intervention will not be known to us.
- \Rightarrow We cannot know the impact of short-term changes in arterial partial pressure of carbon dioxide on patient outcomes.

data mining, Al trair cerebral ischaemia (DCI) and poor neurological outcomes.¹²

ß Physiologically, the detrimental effect of SHV is mediated by carbon dioxide (CO_{a}) , which is the byproduct of cellular respiration. <u>0</u> CO₉ can diffuse across the vessel walls under a concentration gradient and adjust the cerebrovascular tone by changing perivascular pH.^{3 4} The rapid decrease of arterial partial pressure of arterial carbon dioxide $(PaCO_2)$ og caused by hyperventilation would lead to g cerebral vasoconstriction and reduction of **8** cerebral blood flow (CBF), and might serve as a compensatory response for intracranial pressure (ICP) autoregulation to decrease the elevated ICP.⁵⁶ However, over time, its effect on reducing ICP might be attenuated by the cerebrospinal fluid (CSF) buffering effect.⁷ Moreover, CBF can be reduced by 3% for every 1 mm Hg decrease in PaCO₉, and prolonged hyperventilation may increase the

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risk of cerebral ischeamia and cerebral infarction,⁸ which indicates that it produces more harm than good. And induced hypercapnia has been proposed as a treatment in patients with SAH,⁹ therefore, we speculate that therapeutic interventions to minimise SHV might mitigate the cerebral vasospasm and increase CBF, but this speculation has not yet been validated clinically.

IV opioids are commonly used to provide analgesia and supplemental sedation. Dose-dependent respiratory depression is one of the side effects of opioids. Remifentanil is one of the commonly used opioids in intensive care unit (ICU). It could reduce the respiratory rate (RR) by prolonging the expiratory time in a dose-dependent fashion while preserving the respiratory drive, and consequently, minute ventilation (MV) decreases and PaCO_a increases.¹⁰¹¹ Besides, remifentanil is highly lipophilic and has a rapid penetration of the blood-brain barrier. It has a rapid onset of action $(1-2\min)$, and the plasma concentration can reach a steady state within 1 min following the infusion starting or dose adjusting.^{10 12} Its action will disappear in 5-10 min after cessation of infusion as it can be metabolised by esterase widely located in plasma, erythrocytes and interstitial tissues.¹³ Dosedependent RR suppression and an almost instantaneous 'on and off' predictable effect makes titration of remifentanil an ideal option for correcting hyperventilation in aSAH.

The primary purpose of this study is to evaluate the efficacy and safety of remifentanil dose titration in correcting SHV in aSAH. Our goal is trying to maintain PaCO_a in the normal range (35-45 mm Hg) with remifertanil dose adjustments in patients with aSAH with hyperventilation. Changes in PaCO_a and CBF before and after drug intervention at different dosages will be recorded and compared.

METHODS AND ANALYSIS Study design and hypotheses

The design of the study was open-label, unblinded and single group assignment. And it is physiological study to explore the efficacy and safety of remifentanil dose titration in correcting SHV in patients with aSAH. We hypothesised that SHV would be alleviated or corrected by titrating the dose of remifentanil, thereby the decrease in CBF caused by hyperventilation will be ameliorated.

Study population

All adult patients admitted to the ICU of Beijing Tiantan Hospital will be screened for eligibility during January 2021 and December 2022. Written informed consents will be obtained from the patients or their next of kin before inclusion into the study.

Inclusion criteria

1. Emergency admission for aneurysm subarachnoid haemorrhage.

- 2. Undergoing surgery within 3 days of aneurysm rupture.
- 3. No more than 96 hours after clipping and craniotomy for aneurysm.
- 4. Invasively mechanically ventilated with the mode of pressure support (PSV) or continuous positive airway pressure (CPAP).
- 5. The airway occlusion pressure $(P_{0,1})$ greater than 2 cm-H_oO.

- H₂O.
 6. Arterial blood gas (ABG) analysis indicates hyperventilation (tachypnoea combined with PaCO₂ <35 mm Hg and pH >7.45).
 7. With continuous ICP monitoring.
 Exclusion criteria

 Age <18 years.
 Pregnancy.
 Allergic to opioids.
 Clinically relevant of chronic obstructive pulmonary disease (GOLD definition), severe hepatic dysfunction (Child-Pugh class C), serious renal dysfunction (understand discussed discus g dergoing dialysis before surgery), or low likelihood of survival for more than 24 hours.
- uses related to 5. Haemodynamic instability (vasoactive drug infusion except for dopamine at an infusion rate <5µg/kg/ min).
- 6. ICP >20 mmHg.
- 7. Patients or their next of kin refusing to participate in the study.

text In our centre, at least one ABG analysis (Radiometer, ABL90, AQM) will be performed per day. Once SHV is present and other inclusion criteria are met, the patient will be included.

Study intervention

ng, For all the screened patients with aSAH, their routine treatments will be determined by the attending physician, training and will comply with the guidelines of the Neurocritical Care Society and American Heart Association.^{14 15} A flow chart of the study procedure is shown in figure 1.

In our centre, the depth of sedation and pain will be routinely assessed by Richmond Agitation-Sedation Scale (RASS) and Critical Care Pain Observation Tool (CPOT), with targeted values of -2 to 0 and 0-1, respectively.^{16 17} For this purpose, Midazolam and/or Butorphanol will be used before the protocol initiation to achieve the targeted values of RASS and CPOT, and maintained constant during the whole study period. On this basis, the remifentanil will be added to control breathing. The **g** other sedatives and analgesia will be avoided. Antipyretics and/or surface cooling devices will be used to keep the body temperature <37.5°C.

The mechanical ventilation mode (PSV or CPAP) and parameters will be determined by the attending physician. It is common practice that the inspiratory support is set to obtain a tidal volume of 6-8 mL/kg of ideal body weight and RR below 30 breaths/minute, the positive endexpiratory pressure and fraction of inspiration oxygen

and data mini

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Figure 1 Flow chart of the study procedure.

are adjusted according to the ARDSnet table¹⁸ to maintain the saturation of pulse oxygen (SpO₂) at 88%–95% or partial pressure of arterial oxygen at 55–80mm Hg. And the ventilator parameters at enrolment will remain unmodified throughout the study period. The P_{0.1} will be measured as an indicator of spontaneous breathing drive¹⁹ and patients with P_{0.1} <2 cmH₂O at enrolment will be excluded. The end-tidal CO₂ partial pressure (ETCO₂) will be monitored continuously using a mainstream device, and the airway adapter will be placed at the end of the endotracheal tube (CARESCAPE R860).

Remifentanil will be diluted with saline to the required concentration $(50 \,\mu\text{g/mL})$ and intravenously infused through a syringe pump. In view of the rapid onset and offset of action of remifentanil, a 30 min infusion period of remifentanil was determined.^{10 12} The efficacy of remifentanil might vary among individuals. In patients who were mechanically ventilated, the MV would decrease when the infusion rate of remifentanil is higher than $0.05 \,\mu\text{g/kg/min}$. When the dose is higher than $0.10 \,\mu\text{g/kg/min}$, the spontaneous breathing rate may be significantly slowed down.¹² Therefore, the maximum dose of remifentanil was up to $0.08 \,\mu\text{g/kg/min}$ to preserve the patient's ability to breathe spontaneously as much as possible. A

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continuous infusion was started at $0.02 \,\mu\text{g/kg/min}$ and increased to 0.04, 0.06, $0.08 \,\mu\text{g/kg/min}$, each lasting 30 min. The procedure for remiferitanil titration is shown in figure 2.

ICP will be monitored continuously using a microtransducer probe placed in the subdural or ventricle (Integra LifeSciences Corporation, Codman) at the discretion of the treating neurosurgeons. For patients with an external ventricular drain tube, the pressure transducer will be positioned at the level of external auditory meatus. For ICP measurements, the stopclock will be turned off to the drain and opened to the transducer until the ICP reading is stabilised.²⁰

The decrease of CBF due to constriction of cerebral vessel bed caused by hyperventilation has been proved. We would like to explore whether it can be mitigated throughout the intervention, therefore, we will measure the CBF. Hypocapnia reduced the diameter of small cerebral vessels, the diameters of large vessels, such as the internal carotid artery (ICA) and the middle cerebral artery (MCA) would not change significantly. Therefore, the changes in cerebral blood flow velocity (CBFV) of ICA and MCA are linearly correlated to the changes r uses in CBF. And the relative change in CBFV measured by transcranial doppler (TCD) has a good correlation with that measured by magnetic resonance.²¹ We will monitor the CBFV of the ICA and MCA (M1 segment) with TCD (Compumedics, DWL, OL software), which is noninvasive, available at bedside.²¹ CBFV will be measured three times at intervals of 1 min at each remifentanil dose. And TCD measurements will be carried out by two trained researchers. One will perform the measurements, and the other one will assist in supervising the standarda isation of the measurement process and the accuracy of the data.²² Lindegaard ratio, the ratio of the mean flow velocities (MFVs) in MCA and the ipsilateral extracranial ICA, is a common indicator of vasospasm if the value exceeds 3.²³ In case of suspected vasospasm, the digital subtraction angiography or CT angiography and CT perfusion imaging would be performed for confirmation at the discretion of treating physician.

The transient hyperaemia response test (THRT) will be performed according to the method described previously, and will be used to assess cerebral autoregulation.²⁴ When probing the MCA, compress the ipsilateral common carotid artery for 5–9 s. After release of the carotid artery, the first systolic flow velocity (FV) peak will be ignored, and the following three systolic FV peak will be kept. The test will be repeated for three times with an interval of 1 min, and the results of three measurements will be averaged for analysis.²⁵ The THRT is considered normal if the



MCA peak flow rate increased by more than 9% from the baseline value, indicating intact autoregulation.²⁶

The interruption of the study intervention

The study protocol will be interrupted if ICP exceeds 25mm Hg for more than 5min.²⁷ Any of the following conditions occurred and lasted more than 3 min: RR <10 breaths/min; ETCO₂ >40 mm Hg; SpO₂ <90%.¹⁰ Systolic arterial pressure drops below 80mm Hg, mean arterial pressure drops by more than 25% from baseline or cerebral perfusion pressure $\leq 70 \text{ mm Hg}$.

Outcome measurements

The primary outcome of this study is the change in PaCO₉ with different doses of remifentanil (baseline and 30 min after each remifentanil infusion rate adjustment). The secondary outcome is the change in CBF during the intervention. The time points for data collection are shown in figure 2.

Data collection

Data are prospectively collected by trained researchers. Demographic data (age, sex, body mass index, tobacco use, alcohol abuse), comorbidities (diabetes, hypertension, coronary artery disease), primary diagnosis, symptoms of the aSAH (headache, seizures, unconscious, nausea and vomit, neurological deficit) and information about the surgery (operation time, surgical site, surgical approach, indwelling drainage tubes, the location of ICP probes) will be collected.

The World Federation of Neurosurgical Societies scale,²⁸ the Hunt-Hess score²⁹ and the modified Fisher Scale³⁰ will be evaluated on hospital admission to assess the severity of aSAH. The Acute Physiology and Chronic Health Evaluation II score,³¹ Sequential Organ Failure Assessment score³² on the first day of ICU will be used to assess the severity of the disease, and the worst values of the parameters of that day will be used to calculate the scores.

Heart rate, arterial systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP), cerebral perfusion pressure (CPP) (CPP=MAP-ICP), SpO₂ (GE Healthcare, B105) and the Glasgow Coma Scale (GCS) will be routinely monitored and recorded during ICU stay.

Prior to the study intervention, baseline ABG, ICP, vital signs, CPOT score, RASS, GCS, the use of sedatives and analgesics, ventilation modes and parameters, as well as the time of PSV or CPAP mode lasting before the intervention will be recorded. Ten consecutive respiratory cycles will be monitored to record the baseline RR and MV. The mean tidal volume and mean ETCO₉ of 10 breaths will be calculated and recorded. Considering the significant breath-to-breath variability, the value of P_{01} will be taken from an average of 3-4 measurements.

MFV of bilateral MCA and ICA, the Lindegaard ratio and the THRT test measured by TCD will also be recorded.

For safety of patients, the indicators including ICP, vital signs, CPOT score, RASS, GCS, P₀₁ will be recorded repeatedly after each remifentanil dose adjustment.

Patients will be followed until hospital discharge or death, whichever comes first. The vasospasm, DCI and neurological outcome (modified Rankin score) at hospital discharge will be recorded.³³

Definition

- 1. SHV: defined as the tachypnoea combined with the presence of at least one ABG with both $PaCO_{2} < 35 \text{ mm}$ Hg and pH >7.45²
- 2. Chronic obstructive pulmonary disease (COPD): a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both 8 progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.³⁴
- 3. Severe hepatic dysfunction: Child-Pugh class C.
- 4. Serious renal dysfunction: receiving chronic dialysis.
- 5. Haemodynamic instability: requires vasoactive drugs to maintain blood pressure (except for dopamine at an infusion rate $<5 \mu g/kg/min$).¹⁰
- 6. TCD vasospasm: is defined as a MFV in MCA > 120 cm/sec or the Lindegaard ratio >3.35
- 7. Symptomatic vasospasm: refers to the development of new focal neurological signs, deterioration in the level of consciousness, or both, when the cause is felt to be attributable to vasospasm.³⁶
- 8. DCI: defined as symptomatic vasospasm or the appearance of a new infarction on CT or MRI.³⁶

When diagnosing symptomatic vasospasm and delayed cerebral ischaemic injury, it is necessary to exclude a secondary neurological deterioration caused by other factors, such as fever, infectious complications, hydrong, cephalus, epilepsy, respiratory failure and electrolyte disturbances.

Data management and monitoring

AI training The collected data will be stored in a dedicated computer, and a password will be set to ensure the safety of the data. Related paper records including case report form will be stored in a locked cabinet in an access-controlled room guarded by video cameras. The investigators have access to the final trial dataset. The investigators will submit a tracking review to the Institutional Review Board (IRB) of Beijing Tiantan hospital regularly for monitoring **D** the experimental progress. Adverse effects of drug and **g** reasons for interruption of the protocol will be documented and reported to the IRB of Beijing Tiantan Hospital within 24 hours, and no interim analysis will be scheduled.

Current sample size justification

The trial is an exploratory physiological study. A total of 120 patients with aSAH were admitted to our centre in 2020. In previous studies, the incidence of SHV was 55%-83% among patients with aSAH. Therefore, the investigators predict that a total of approximately 30 patients will be enrolled during the scheduled period considering the inclusion criteria.

Statistical analysis

The data of patients interrupted by adverse events will be included in the final analysis. Continuous variables will be expressed as mean and standard deviation, and compared using t-test. Non-parametric variables will be expressed as a median and interquartile range, and compared using Wilcoxon rank-sum test. Categorical variables will be expressed as absolute (n) and frequency (%), and compared using χ^2 test. All PaCO₂ and CBF values (at the end of each infusion rate) will be compared with baseline value with one-way analysis of variance for repeated measurements and Dunnett's multiple comparisons test. Besides, the difference in PaCO₉ and CBF between the measurements at respective time points and baseline value will be calculated and analysed to demonstrate the effect of variable doses of remifentanil. And subgroup analysis will be conducted to compare the amount of remifentanil among patients with different severity.

All analyses will be performed using GraphPad Prism V.4.0 statistical software. Two-tailed p values <0.05 would be considered statistically significant for all comparisons.

Ethics and dissemination

The study has been approved by the IRB of Beijing Tiantan Hospital, Capital Medical University (KY 2021-006-02), and has been registered at ClinicalTrials.gov (id: NCT04940273). The results of the study will be presented in the form of peer-reviewed publications and conference presentations.

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.

Summary

Transient hypocapnia may benefit for ICP.^{6 33} However, Coles and colleagues reported that even a brief period of moderate hypocapnia ($PaCO_2 < 34 \text{ mm Hg}$) could result in a significant increase in the volume of critically hypoperfused tissue in the damage region.^{37 38} And in patients with aSAH, the phenomenon SHV is common and is associated with poor prognosis.⁵

However, there is currently no conclusion on how to correct SHV in patients with aSAH safely and effectively. Remifentanil is an ultra-short-acting opioid analgesic, and is commonly used in the ICU. It seems to be an ideal choice because it can depress respiration in a dose-dependent fashion. In addition, it has a rapid onset of action, a short half-life, and can quickly reach a steady-state concentration after dose adjustment, as well as its efficacy. However, no known trials or evidence-based guidelines have demonstrated the safety and efficacy of remifentanil for correction of SHV in patients with aSAH. This study intends to investigate the effect of different doses of remifentanil on

PaCO₉, to assess the safety and effectiveness of the method, and to explore the optimal range of safe dose. In addition, the effects of different doses of remifentanil and its induced PaCO₉ changes on cerebral haemodynamics and cerebral autoregulation will also be assessed.

In this trial, we choose a starting dose of $0.02 \mu g/kg/$ min to ensure the safety of patients, and then escalated the dose to 0.04, 0.06, 0.08µg/kg/min, each lasting 30min. ETCO₉ will be monitored during the intervention to avoid CO₉ retention. Once the ETCO₉ exceeds 40 mm Hg, RR **u** lower than 10 breaths/min or SpO₉ drops below 90% and the conditions last more than $3 \min$, the intervention will be terminated and the ventilator mode will be adjusted to ensure the safety of participants. We will also evaluate other adverse effects that may result in the intervention. We will 8 monitor the invasive arterial blood pressure continuously to avoid hypotension caused by the vagomimetic effect of **a** remifentanil.¹² If the MAP drops by more than 25% from baseline or CPP ≤70 mm Hg, the remifentanil infusion rate will be reduced to previous dose or interrupted completely, and the investigators will reassess the MAP and CPP every 2 mins until it returns to the normal range.³⁹

We hypothesised that the correction of hypocapnia might We hypothesised that the correction of hypocapnia might improve CBF and be beneficial to patients with aSAH. Improve CBF and be beneficial to patients with aSAH. However, this may not be the case. Previous studies have shown that reduced CBF may be restored to baseline 30min after the onset of hypocapnia in brain-injured patients, ⁴⁰ of the MPACO₂. During the study intervention, transient CO₂ fluctuations due to repeated patients awakening for full addition, correction of hypocapnia may lead to an actuation recease in cerebral blood volume and ICP. Therefore, we will monitor the ICP continuously during the intervention. If the ICP exceeds 25mm Hg for more than 5min, the directly generalised to other centres. Furthermore, since this is a single-centre study, so the results may not be directly generalised to other centres. Furthermore, since that a single control of hypocapnia by continuous remiferiating infusion on the prognosis of patients with aSAH. However, from this study, we can learn about the efficacy future studies on long-term intervention.
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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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