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Choice of ANesthesia for EndoVAScular Treatment of Acute Ischemic Stroke at Posterior Circulation (CANVAS II): Protocol for an Exploratory Randomized Controlled Study

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ABSTRACT

Introduction

Observational studies indicate that the type of anesthesia may be associated with the post-procedural neurological function in patients with acute ischemic stroke patients undergoing endovascular treatment. Patients with acute posterior circulation ischemic stroke may experience different physiological changes and result in severe neurological outcome. However, the effect of the type of anesthesia on post-procedure neurological function has remained unclear.

Methods and analysis

This is an exploratory randomized controlled trial which will be carried out at Beijing Tiantan Hospital, Capital Medical University. Patients with acute posterior circulation ischemic stroke and deemed suitable for emergency endovascular recanalization will be recruited in this trial. Eight-four patients will be randomized to receive either general anesthesia or local anesthesia/conscious sedation with 1:1 allocation ratio. The primary endpoint is the 90-day modified Rankin Score postoperatively.

Ethics and dissemination

The study is registered at the ClinicalTrial.gov (NCT03317535) and has been reviewed by and approved by Ethics Committee of Beijing Tiantan Hospital of Capital Medical University (KY2017-074-02). If the results are positive, the study will indicate that whether the type of anesthesia affects neurological outcome after endovascular treatment. The findings of the study will be published in peer-reviewed journals and will be presented at national or international conferences.

Trial registration number: NCT03317535

Keywords

General anesthesia, Local anesthesia, Conscious sedation, Endovascular treatment, Posterior circulation, Acute ischemic stroke, Neurological outcome

Article Summary

Strengths and limitations of this study

- This is the first randomized control study to determine the effect of anesthesia modality on neurological outcome on patients with posterior circulation acute ischemia stroke.
- The findings of the study would contribute to being as a reference for a future multi-centric trial to verify the effects of anesthesia on patients with posterior circulation AIS undergoing EVT.
- One limitation of the study is it is a single-centered trial. Future multi-centric trial is need to verify the effects of anesthesia on patients with posterior circulation acute ischemia stroke undergoing endovascular treatment.

INTRODUCTION

Acute ischemic stroke (AIS) at posterior circulation account for 17%-60% of acute ischemia stroke with difficulty in treatment, which result in poor outcomes and a high mortality of 80%-95%[1-5]. Early recanalization is one of the most important predictors of favorable outcome for posterior circulation AIS patients at 90 days [6]. Though endovascular therapy (EVT) has been demonstrated to be an effective and safe treatment for patients' neurological function with around 30% good clinical outcome improvement and 35% mortality decrease at 90 days after interventional procedure, there is a substantial proportion of patients suffered from poor clinical outcomes even undergoing timely successful reperfusion[7-10]. Many factors may contribute to the mismatched association of high reperfusion rate and poor clinical outcome, including patient-specific factors (age, collaterals status, initial stroke severity, infarct volume and site, and distal artery emboli, etc.), procedural-specific factors (time from onset to recanalization, degree of recanalization) and anesthesia management[2 11 12].

The optimal anesthesia choice and management for AIS patients during EVT, general anesthesia (GA) or local anesthesia/conscious sedation (LA/CS), is still remain unclear. Benefits of GA with tracheal intubation or laryngeal mask include secured airway to avoid aspiration, body immobility to avoid intracranial vessel perforation and better digital subtraction angiography imaging. On the other hand, hypotension, nosocomial infection, delayed procedure initiation and neurological evaluation, and hyperventilation may contribute to poor outcomes, even yielding devastating complications. LA/CS management permits neurological function assessment, shortens mean time from door to groin puncture and minimizes hemodynamic changes associate with airway manipulation. However, the risk of aspiration and substantial movement during endovascular procedural are the main two disadvantages associated with LA/CS [13-15].

Three randomized controlled trials have compared the neurological outcomes after EVT with GA or LA/CS in AIS patients. The Sedation vs. Intubation for Endovascular

Stroke TreAtment (SIESTA) trial reported similar National Institute of Health stroke scale (NIHSS) scores at 24 hours between GA and LA/CS, but favorable outcomes, measured by modified Rankin scale (mRS) score was found in patients with GA 3 months after treatment[14]. Similarly, the General Or Local anesthesia in Intra Arterial THerapy (GOLIATH) trial reported growing brain infarct volume decreased and favorable 90-day mRS score increased with GA [16]. However, The Anesthesia during Stroke (AnStroke) trial reported no difference between GA and LA/CS in 90-day mRS[17]. Recently, a meta-analysis using fixed-effects model by obtaining individual patient data from the above-3 trials with blinded endpoint evaluation, indicated that significantly different results in favor of the GA group (cOR=1.58, 95%CI: 1.09-2.29)[18]. Nevertheless, these findings should be interpreted with caution. Firstly, these trials only provided insight into choice of anesthesia modality in the anterior circulation AIS population, the result of above researches are not appropriate for patients with posterior circulation occlusions. Secondly, only AnStroke trial analyzed the neurological function at 90 days as the primary outcome, while in other 2 trials, it was analyzed as as the secondary outcome. Hence the conclusion on relationship between anesthesia and neurological function at 90 days should be drawn with caution [17]. Therefore, result of above trials is not suitable for posterior circulation AIS, concerning the relationship between neurological outcome and anesthesia modality.

A few studies observed the feasibility of monitoring anesthesia care for elective endovascular procedures either in anterior or posterior circulations, and demonstrated high technical success with low rates of peri-procedural complications and mortality[19] [20]. Although theses study included a relatively large proportion of posterior circulation interventions and showed promising results, it is unreasonable to employ previous results in emergent setting, with potential presence of severe brain stem ischemia. Moreover, only one study focused purely on the posterior circulation patients and investigated the influence of anesthesia modality and management on clinical and angiographic outcomes[19]. In this retrospective, matched, observatory study, LA/CS was found to be feasible and appeared to be as safe and effective as GA. However,

retrospective design and relatively limited sample size may introduce undetected biases. Furthermore, there is no randomized controlled trial to study whether GA and LA/CS own the different neurological outcome at 90 days undergoing EVT for posterior circulation AIS.

On the basis of the findings of previous studies, we propose to conduct a trial to compare neurological outcome in posterior circulation AIS patients receiving GA with those receiving LA/CS for EVT.

METHODS

The protocol has been prepared according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[21]. All trial procedures are summarized in Table 1. For completed checklists, see Supplementary file 1.

Study design

This is a randomized, parallel-group, exploratory trial with blinded endpoint evaluation to determine whether GA or LA/CS produces different neurological outcomes in posterior circulation AIS patients undergoing EVT. Posterior circulation AIS patients will be enrolled from Beijing Tiantan Hospital, Capital Medical University from 2018 to 2020. This trial was approved by the Ethics Committee of Beijing Tiantan Hospital of Capital Medical University (KY2017-074-02) and registered in www.clincaltrials.gov (NCT03317535). The participants flowchart is briefly illustrated in Figure 1

Participants

Posterior circulation AIS Patients who deemed suitable for recanalization of the culprit's vessels will be considered for recruiting the study. The inclusion criteria are vertebral artery and/or basilar artery responsible for posterior circulation ischemia confirmed by CTA/MRA, age $\geqslant$18 years, stroke onset to treatment time $\leqslant$ 24 hours, modified Rankin Score$\leqslant$2 before onset.

Patients with unclear radiological image to identify infarction and vessel occlusion, with intracranial hemorrhage, anterior circulation occlusion, Glasgow coma score ⩽ 8, NIHSS score < 6 or > 30, severe agitation or seizures, loss of airway protective reflexes and/or vomiting on admission, intubated before EVT, and known allergy to anesthetics or analgesics will be excluded from the study. Both the neuro-radiologists and the attending anesthesiologists must agree that the patient is suitable with either GA or LA/CS management before recruiting. The reasons that eligible patients are not recruited to the trial will be documented.

Randomization and blinding

Randomization occurs on the time of EVT when patients are sent to the interventional neuroradiology suite, the decision for EVT has been made, and written informed consent is obtained from patient or his/her legal representatives. Randomization will be conducted via a computer-generated table. Patients will be randomly allocated to receive either GA or LA/CS in a 1 to 1 ratio. A designated staff who will neither involved in anesthesia management nor follow-up will perform recruitment as well as allocation randomization sequence. This designated staff will implement the allocation sequence through opaque, sealed and stapled envelopes. The endpoint assessors will be blinded to the randomization group.

Standard operating procedures are applied to both groups to ensure no principal differences generated and uniform protocol implemented. The outcome assessors are blinded to the information of treatment for the enrolled patients and will evaluate the outcome variables for this study to ensure unbiased reporting. The anesthesiologist, neuro-radiologist as well as attending doctors in neurological intensive care unit (NICU) will not be blinded as they need to participate in the safe administration of GA or LA/CS and related medical care. The enrolled patients and his/her legal representatives will not be blinded, either.

Interventions

GA and LA/CS in this trial are defined according to the Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists due to the continuum ranging of level of sedation from minimal sedation to GA[22]. In LA/CS group, patients will receive sedative drugs if necessary but still following instruction to verbal stimulation. Patients with LA/CS will follow the sedation protocol as following: bolus propofol of 0.3-0.5mg/kg, following continuous propofol infusion of 1-2 mg/kg/h and remifentanil infusion of 0.01-0.06 ug/kg/min while saturation of pulse oximetry (SpO_2) will be kept above 94% with inhaled oxygen flow at 3L/min and end-tidal carbon dioxide ($ETCO_2$) monitored via nasal cannula [23 24 13]. The bispectral index (BIS) value will be maintained above 70 via adjusting the infusion of sedative drugs.

In GA group, patients will receive rapid sequence induction with endotracheal intubation or laryngeal mask implementation with propofol, remifentanil and muscle relaxant. Anesthesia will be induced with infusion of propofol of 1-2mg/kg and remifentanil of 0.2-0.8 ug/kg for anesthesia induction[25]. Muscle relaxation will be achieved with rocuronium (0.6 mg/kg). After endotracheal intubation or laryngeal mask implementation, mechanically ventilation will initiate to achieve normocapnia with a 40%-60% fraction of inspired oxygen. Anesthesia will then be maintained with propofol (4-6mg/kg/h) and remifentanil (0.05 to 0.1 ug/kg/min) infusion to maintain the BIS value between 40 and 60.

Converting from LA/CS to GA is an important issue in this trial. In cases of procedural emergency including vessel perforation, intracranial hemorrhage (ICH), subarachnoid hemorrhage(SAH), seizures, deep coma (GCS decrease to 8), respiratory failure ($PaCO_2 \geqslant 60$ mmHg, or $SpO_2<94\%$ without relevant improvement by increasing inhaled oxygen fraction), cardiovascular fluctuation and severe disturbance of the treatment procedure (vomiting, substantial movement and uncoordinated dysphoria), LA/CS will be converted to GA. The decision to convert from LA/CS to GA will be made by the neuro-radiologist in charge and the attending anesthesiologist. The number of patients and reasons for the conversion will be recorded in detail. A guideline for

airway management on conversion population is listed in Table 2.

Standard anesthesia management protocols during EVT (Concomitant treatment)

All randomized patients will receive standard monitoring, including electrocardiography (EEG), non-invasive blood pressure (BP), heart rate (HR), pulse oxygen saturation (S_PO_2), invasive arterial pressure monitoring, $PaCO_2$, $ETCO_2$, inspired oxygen fraction (FiO_2) and blood glucose. All patients will receive BIS monitoring to assess the depth of sedation or anesthesia with BIS probe placed on the forehead. Physiologic parameters will be recorded using purposely designed data collection table. BP and blood glucose will be controlled according to current guidelines for stroke therapy [24 26]. Specifically, systolic blood pressure (SBP) is aimed to be kept between 140 and 180 mmHg and diastolic blood pressure (DBP) less than 105 mmHg, with phenylephrine or norepinephrine infusion. Plasma glucose will be maintained at level of 140-180 mg/dl and $ETCO_2$ will be maintained between 35 and 45 mmHg, while S_PO_2 is aimed to be over 94%, with FiO_2 at a range from 40% to 60% [25]. It is anticipated that patients in the LA group may deteriorate during EVT and may, therefore, require endotracheal intubation for airway protection.

Measurements

All patients will be regularly visited while in hospital by outcome assessors who are blinded to the treatment allocation. The incidence of complications, including myocardial infarction, non-fatal cardiac arrest, new stroke, pulmonary embolism and deep venous thrombosis will be recorded. All patients will receive brain imaging, including computed tomography (CT), CT angiography (CTA), magnetic resonance (MR) or MR angiography (MRA) before, 24 hours, 7 days (or at discharge, whichever sooner), 30 days and 90 days after randomization. Brain image will be used to assess new brain hemorrhage (if present) and infarct volume. Efficacy of vessels recanalization will be assessed by the modified Thrombolysis in Cerebral Infarction (mTICI) scale. The severity of stroke will be assessed using the NIHSS scale during the same period. Disability will be rated at discharge and three months after EVT and

rated using mRS. To minimize loss of follow-up after discharge, study coordinators will contact the patients and his/her next-of-kin on a weekly basis. Besides, adverse effect will be also recorded.

Study objectives

The study aims to detect the difference of the post-procedural neurological function in patients with posterior circulation AIS under GA and LA/CS, and hence to observe the effect of anesthesia type on outcomes after EVT.

Primary endpoint

The primary endpoint is the neurological disability at 90-day after EVT measured by mRS and a favorable neurological outcome is identified as mRS≤2. The score will be evaluated by outcomes assessor who are blinded to allocation.

Secondary endpoints

The secondary endpoints include the followings:

1. Change in NIHSS before, 24 h, 7 days (or at discharge), 30 days and 3 months after randomization.
2. The score of mTICI will be evaluated before and after endovascular treatment.
3. All-cause mortality up to 3 months after randomization.
4. The incidence of complications up to 3 months after randomization.
5. The length of stay in the hospital or intensive care unit after randomization.
6. The rate of converting from LA/CS to GA.
7. All adverse events associated with this study will be recorded.

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.

Statistical analysis plan

Descriptive statistics will be reported as means with standard deviation and medians with interquartile range for normally distributed data and skewed continuous data, respectively, and counts (percentage) for categorical data. The analysis will be based on intention-to-treat. Differences in the primary endpoint will be compared between groups using Cochran-Mantel-Haenszel test. Furthermore, primary outcome will be analyzed in following subgroups: age, gender, baseline NIHSS score; time from onset of stroke to EVT, site of arterial occlusion, and TICI score. Other categorical variables will be analyzed by χ^2 test and continuous variables using Student-t test or Mann-Whitney U test.

To allow for a varying number of follow-up measurements, the repeated measure ANOVA methods with a mixed model approach (treating time as a random effect and other covariates as fixed effects) will be utilized, and the specific comparison of change in each of those measurements between baseline and any specific post-baseline time point can be tested using linear contrast. In addition, missing data will be imputed using inverse probability weighting and worst case imputation scenarios. STATA 14.0 (StataCorp LP, College Station, TX) for windows will be used for all statistical analyses. The statistical significance will be declared at type I error of 0.05.

Sample size calculation

The PASS 15 software (NCSS, LLC, USA) is used to calculate the sample size based on the primary endpoint – favorable outcome (mRS 0-2) at three months after randomization. Several trials focused on the neurological outcome of patients with posterior circulation AIS, however, only two indicated the association between anesthesia type and neurological outcome. In the case-control study of Ashutosh et al, they reported the incidence of mRS$\leqslant$2 at 90-day was 38.3% in LA/CS and 31.1% in GA[19]. On the other hand, a retrospective observational study in our institution reported a higher incidence of favorable neurological outcome at 90-day in LA/CS compared to GA group (68.7% vs 35.6%)[27]. However, other factors including pre-operative NIHSS score, pre-operative intravenous thrombolysis treatment et al. confound the results

validity[27]. Meanwhile, in previous anterior circulation research, AIS patients receiving GA presented a favorable or similar neurological outcome at 90 days compared with LA/CS[13 17 28]. Taking this into account, we consider that the sample size to detect 30% difference in mRS 0-2 would require 44 in each group to achieve power of 80% at a two-tailed significant level of 0.05, with a drop-out rate of 5%[29].

Reporting of adverse events

All adverse events associated with this trial will be recorded and closely monitored until resolution or stabilization or until it has been shown that potential conflicts of interest regarding the study treatment are not the cause of the event. The principal investigator is responsible for reporting all adverse events. Once adverse events occur, it should be immediately reported to the research department and informed to the principal investigator to determine the severity of the adverse events and their consequence of the injury. All adverse events associated with this study will be recorded and reported to the Ethics Committee within 24 hours.

Protocol Amendment

The chief investigator will be responsible for any decision to amend the protocol. If there is any modification (eg, changes to eligibility criteria, outcomes, analyses) the principle investigator will communicate and gain approval from the Ethical Committee of Beijing Tiantan Hospital, Capital Medical University prior to implementation, and communicate with relavant parties.

Ethics and dissemination

The approval for the study was certificated by the Ethical Committee of Beijing Tiantan Hospital, Capital Medical University on 19 December, 2017 (reference number: KY2017- 074-02). The study was registered on clincaltrials.gov on 23 October, 2017 (NCT03317535). The study recruited the first patient on 1 February, 2018, and the estimated study completion date will be 31 Dec, 2020.The findings of the study will be published in peer-reviewed journals and will be presented at national or international conferences.

DISCUSSION

This is an exploratory controlled randomized study aiming to detect the effect of anesthesia choice on the neurological outcome in the patients with posterior circulation AIS undergoing EVT. The study aims to test the hypothesis that GA and LA/CS have different effects on the post-endovascular procedure neurological outcomes in patients with posterior circulation AIS.

Anesthetic selection and peri-procedural management appear to be closely associated with outcomes in patients with posterior circulation AIS undergoing EVT. The hemodynamics disturbance and the changes in $ETCO_2$ may be associated with the poor outcomes. However, no consistent agreement about the anesthesia modality has been reached, the anesthetic protocols varies among different stroke centers. In daily clinical work, the actual practice of anesthesia for EVT, especially for posterior circulation AIS patients, largely base on local protocols and individual preference of neuro-radiologists or anesthesiologists. LA/CS may be used for cooperative patients and GA for severely agitated, non-conscious and unprotected airway patients[13]. A small number of retrospective studies (concluding patients with posterior circulation AIS) show that LA/CS groups have better clinical outcomes, lower complication rate, shorter reperfusion time and less changes in hemodynamics and respiration[19 20 27]. In contrary, GA groups suffer from worse neurological function, lower blood pressure, aspiration pneumonia and/or high mortality [30-37]. A recent retrospective, matched, case-control study of patients with posterior circulation AIS is the only study to detect the effect of anesthesia management on outcome of patients with posterior AIS, however, great limitation and drawbacks in terms of study design, including selection bias and information bias impede the credibility of the results[19]. As to above, several confounding factors contribute inconclusive results, including specific information of peri-interventional management, such as blood pressure, partial pressure of carbon dioxide, and strict uniform anesthesia protocol, etc. Therefore, a prospective, randomized, controlled trial is required to account for the peri-procedural confounders and demonstrate the effects of anesthesia (type and management) on outcomes for

patients with posterior AIS undergoing EVT.

This trial aims to find the effect of anesthesia choice on the post-endovascular procedure outcomes in patients with posterior circulation AIS using a randomized controlled trial design. The features of the current study involve strict randomized system, clear inclusion and exclusion criteria, a rigorous uniform protocol to manage hemodynamic, respiratory parameters and blood glucose in GA and LA/CS group, and full-time attending anesthesiologists in each procedure. The findings of the study would contribute to being as a reference for a future multi-centric trial to verify the effects of anesthesia on patients with posterior circulation AIS undergoing EVT.

Patient and public involvement

Patients and the public were not directly consulted in the development of the research question or outcome measures. Patients were not involved in the design, the recruitment and conduct of the study. At the completion of this trial, a manuscript will be prepared to present the trial results. Results of the final study will be disseminated to all study participants through their preferred method of communication indicated at the time of enrollment. The burden of intervention will not be taken by participants themselves.

Competing interests

None declared.

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Author contributions

FL and YZ conceived the study. FL, YZ, SL, ZM, YP and RH initiated the study design and helped with protocol development and implementation. FL, YX, YW, YZ and MJ helped in data collection and manuscript revision. YP and RH are the grant holders. FL and YZ are the co-first authors. YP is the responsible author. All authors contributed to refinement of the study protocol. All authors have read and approved the final manuscript.

Ethics approval

This study is approved by the Ethical Committee of Beijing Tiantan Hospital, Capital Medical University (reference number: KY2017- 074-02).

Data sharing statement

This manuscript is a protocol for a randomized controlled trial, which does not include data.

List of tables and figures:

Table 1. Schedule of enrollment, intervention and assessment.

Table 2. Guidelines for airway management in local anesthesia/conscious sedation group

Figure 1. CONSORT flow diagram for CANVAS II clinical trial.

Supplementary file 1 SPIRIT checklist.

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Table 1. Schedule of enrollment, intervention and assessment.

	STUDY PERIOD							
	Enrolment	**Allocation**	**Post-allocation**					
TIMEPOINT	***At arrival***	**After evaluation**	***During treatment***	***24h after treatment***	***7 days after treatment***	***Discharge***	***30 days after treatment***	***90 days after treatment***
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
INTERVENTIONS:								
GA			X					
LA/CS			X					
ASSESSMENTS:								
Baseline variables	X	X						
Brain image	X			X				
mRS							X	X
NIHSS	X			X	X		X	X
mTICI			X					
All-cause mortality								X
length of stay								X
ICU stay and length								X
Converting rate			X					
Adverse event			X					X

GA: general anesthesia; LA/CS: local anesthesia/conscious sedation; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin Score; mTICI: modified Thrombolysis in Cerebral Infarction Scale

Table 2 Guidelines for airway management in local anesthesia/conscious sedation group.

A. Criteria for tracheal intubation

a. Unconscious with GCS score <8 points;

b. Increase of $ETCO_2$ >60 mmHg and/or a decrease in S_PO_2<94% despite oxygen supplementation;

c. Agitation that cannot be controlled with sedation and/or restraint;

d. Seizure attack;

e. Vomiting;

f. Recognized complications from endovascular therapy, such as vessel puncture leading to intracerebral hemorrhage or subarachnoid hemorrhage.

B. Tracheal intubation, with or without anesthetic agents, may be performed.

C. Anesthetic agents, including propofol or barbiturate infusion, with or without muscle relaxants could be used so that patients will tolerate tracheal intubation and allow effective lung ventilation.

GCS: Glascow coma scale; S_PO_2: pulse oxygen saturation; $ETCO_2$: end-tidal carbon dioxide.

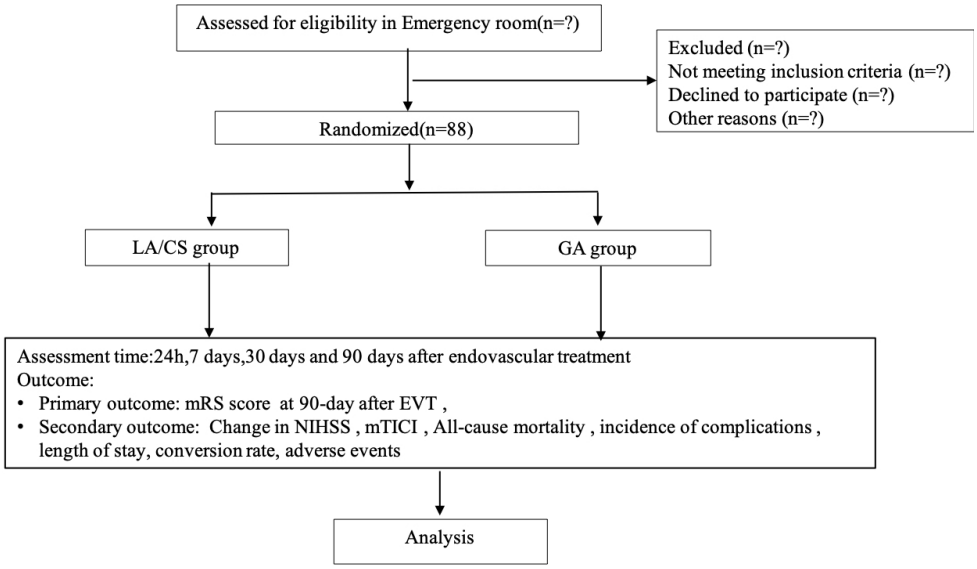

Figure 1. CONSORT flow diagram for CANVAS II clinical trial.

Figure 1. CONSORT flow diagram for CANVAS II clinical trial.

216x142mm (150 x 150 DPI)

Additional file 1: SPIRIT checklist.

Section/item	ItemNo	Description	page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1,7
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,15
	5b	Name and contact information for the trial sponsor	1,15

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5-6
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8,11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10, Table 1
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	NA
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

BMJ Open

Choice of ANesthesia for EndoVAScular Treatment of Acute Ischemic Stroke at Posterior Circulation (CANVAS II): Protocol for an Exploratory Randomized Controlled Study

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Choice of ANesthesia for EndoVAScular Treatment of Acute Ischemic Stroke at Posterior Circulation (CANVAS II): Protocol for an Exploratory Randomized Controlled Study

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ABSTRACT

Introduction

Observational and interventional studies indicate that the type of anesthesia may be associated with the post-procedural neurological function in patients with anterior circulation acute ischemic stroke undergoing endovascular treatment. Patients with acute posterior circulation ischemic stroke may experience different physiological changes and result in severe neurological outcome. However, the effect of the type of anesthesia on post-procedure neurological function remained unclear in this population.

Methods and analysis

This is an exploratory randomized controlled trial that will be carried out at Beijing Tiantan Hospital, Capital Medical University. Patients with acute posterior circulation ischemic stroke and deemed suitable for emergency endovascular recanalization will be recruited in this trial. Eighty-four patients will be randomized to receive either general anesthesia or conscious sedation with 1:1 allocation ratio. The primary endpoint is the 90-day modified Rankin Scale.

Ethics and dissemination

The study is registered at the ClinicalTrial.gov (NCT03317535) and has been reviewed by and approved by Ethics Committee of Beijing Tiantan Hospital of Capital Medical University (KY2017-074-02). If the results are positive, the study will indicate whether the type of anesthesia affects neurological outcome after endovascular treatment of posterior stroke. The findings of the study will be published in peer-reviewed journals and presented at national or international conferences.

Trial registration number: NCT03317535

Keywords

General anesthesia, Conscious sedation, Endovascular treatment, Posterior circulation, Acute ischemic stroke, Neurological outcome

Article Summary

Strengths and limitations of this study

- This is the first randomized control study to observe the effect of anesthesia modality on neurological outcome of patients with posterior circulation acute ischemic stroke.
- The findings of the study would contribute to serve as a reference for a future trial to verify the effects of anesthesia on patients with posterior circulation acute ischemic stroke undergoing endovascular therapy.
- One limitation of the study is it is a single-centered trial. Future multicenter trial is needed to verify the effects of anesthesia on patients with posterior circulation acute ischemic stroke undergoing endovascular treatment.
- The sample size is relatively small and the result will need to be confirmed by larger-size trials.
- Patients are selected mainly based on time window, salvageable ischemic brain tissue and initial infarct size might be considered in the inclusion criteria.

INTRODUCTION

Acute ischemic stroke (AIS) at posterior circulation account for 17%-60% of acute ischemic stroke with difficulty in treatment, which result in a poor outcome and mortality rate of 80%-95%[1-5]. Early recanalization is one of the most important predictors of favorable outcome for posterior circulation AIS patients at 90 days [6]. Though endovascular therapy (EVT) has been demonstrated to be an effective and safe treatment with around 30% good clinical outcome improvement and 35% mortality decrease at 90 days, there is a substantial proportion of patients with poor clinical outcomes even after timely successful reperfusion[7-10]. Many factors may contribute to the mismatched association of high reperfusion rate and poor clinical outcome, including patient-specific factors (age, collaterals status, initial stroke severity, infarct volume and site, and distal artery emboli, etc.), procedural-specific factors (time from onset to recanalization, degree of recanalization) and anesthesia management[2 11 12].

The optimal anesthesia choice and management for AIS patients during EVT, general anesthesia (GA) or conscious sedation (CS), is still unclear. Benefits of GA with tracheal intubation or laryngeal mask include secured airway to avoid aspiration, body immobility to avoid vessel perforation and better digital subtraction angiography imaging. On the other hand, hypotension, nosocomial infection, delayed procedure initiation, loss of neurological evaluation, and hyperventilation may contribute to poor outcomes. CS management permits neurological function assessment, shortens mean time from door to groin puncture and minimizes hemodynamic changes associate with GA. However, the risk of aspiration and substantial movement during endovascular procedural are the main two disadvantages associated with CS [13-17].

Three randomized controlled trials have compared the neurological outcomes after EVT with GA or CS in anterior circulation. The Sedation vs. Intubation for Endovascular Stroke TreAtment (SIESTA) trial reported similar National Institute of Health stroke scale (NIHSS) scores at 24 hours between GA and CS, but favorable outcomes, measured by modified Rankin scale (mRS) was found in patients with GA 3

months after treatment as a secondary outcome measure[14]. Similarly, the General Or Local anesthesia in Intra Arterial THerapy (GOLIATH) trial reported similar brain infarct volume and favorable 90-day mRS score increased with GA[18]. However, The Anesthesia during Stroke (AnStroke) trial reported no difference between GA and CS in 90-day mRS[19]. Recently, a meta-analysis using fixed-effects model by obtaining individual patient data from the above-3 trials with blinded endpoint evaluation, indicated significantly different results in favor of the GA group (cOR=1.58, 95% CI 1.09-2.29)[20]. Nevertheless, these findings should be interpreted with caution. Firstly, these trials only provided insight into choice of anesthesia modality in the anterior circulation AIS population, the result of above researches are not appropriate for patients with posterior circulation occlusions. Secondly, only AnStroke trial analyzed the neurological function at 90 days as the primary outcome, while in other 2 trials, it was analyzed as a secondary outcome. Hence the conclusion on relationship between anesthesia and neurological function at 90 days should be drawn with caution [19].

A few studies observed the feasibility of monitored anesthesia care for elective endovascular procedures either in anterior or posterior circulations, and demonstrated high technical success with low rates of peri-procedural complications and mortality[21] [22]. Although these studies included a relatively large proportion of posterior circulation interventions and showed promising results about feasibility of monitored anesthesia care, it is unreasonable to employ previous results in emergent setting, with potential presence of severe midbrain ischemia. Moreover, only one study focused purely on the posterior circulation patients and investigated the influence of anesthesia modality and management on clinical and angiographic outcomes[21]. In this retrospective, matched, case-control study, CS was found to be feasible and appeared to be as safe and effective as GA. However, retrospective design and relatively limited sample size may introduce undetected biases. Furthermore, there is no published randomized controlled trial that explored whether GA or CS are associated with different neurological outcome at 90 days in patients undergoing EVT for posterior circulation AIS.

On the basis of previous studies, we propose to conduct a trial to compare neurological outcome in posterior circulation AIS patients receiving GA with those receiving CS for EVT.

METHODS

The protocol has been prepared according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[23]. All trial procedures are summarized in Table 1. For completed checklists, see Supplementary file 1.

Study design

This is a randomized, parallel-group, exploratory trial with blinded endpoint evaluation to determine whether GA or CS produces different neurological outcomes in posterior circulation AIS patients undergoing EVT. Posterior circulation AIS patients will be enrolled from Beijing Tiantan Hospital, Capital Medical University from 2018 to 2020. This trial was approved by the Ethics Committee of Beijing Tiantan Hospital of Capital Medical University (KY2017-074-02) and registered in www.clincaltrials.gov (NCT03317535). The participants flowchart is briefly illustrated in Figure 1

Participants

Posterior circulation AIS Patients who deemed suitable for recanalization of the culprit's vessels will be considered for recruitment in the study. The inclusion criteria are vertebral artery and/or basilar artery responsible for posterior circulation ischemia confirmed by computed tomography angiography (CTA)/ magnetic resonance angiography (MRA), the modified Thrombolysis in Myocardial Infarction (mTIMI) score ≤1, age ≥18 years, stroke onset to treatment time ≤ 24 hours, and modified Rankin Score≤2 before onset.

Patients with unclear radiological image to identify infarction and vessel occlusion, with intracranial hemorrhage, anterior circulation occlusion, Glasgow coma score （GCS） ≤8, NIHSS score < 6 or > 30, post-circulation Alberta Stroke Program Early CT Score (pc-ASPECTS) < 6, pons-midbrain index ≥ 3, severe agitation or

seizures, loss of airway protective reflexes and/or vomiting on admission, intubated before EVT, unconsciousness, and known allergy to anesthetics or analgesics will be excluded from the study. Patient whose legal relative refuses to participate will be excluded. Both the neuro-radiologists and the attending anesthesiologist must agree that the patient is suitable with either GA or CS management before recruiting. Reasons why eligible patients are not recruited to the trial will be documented.

Randomization and blinding

Randomization occurs on the time of EVT when patients are admitted to the interventional neuroradiology suite, the decision for EVT has been made, and written informed consent is obtained from patient's legal representatives. Randomization will be conducted via a computer-generated table. Patients will be randomly allocated to receive either GA or CS in a 1 to 1 ratio. A designated staff who will neither be involved in anesthesia management nor follow-up will perform recruitment as well as allocation randomization sequence. This designated staff will implement the allocation sequence through opaque, sealed and stapled envelopes. The endpoint assessors will be blinded to the randomization group.

Standard operating procedures are applied to both groups to ensure no principal differences generated and uniform protocol implemented. Patients in both groups will receive local anesthesia at puncture site, with 3-5 ml of 1% lidocaine hydrochloride prior to arterial puncture. The outcome assessors are blinded to the information of treatment for the enrolled patients and will evaluate the outcome variables for this study to ensure unbiased reporting. The anesthesiologist, neuro-radiologist as well as attending doctors in neurological intensive care unit (NICU) will not be blinded as they need to participate in the safe administration of GA or CS and related medical care. The enrolled patients and his/her legal representatives will not be blinded, either.

Standard anesthesia management protocols during EVT (Concomitant treatment) All randomized patients will receive standard monitoring, including electrocardiography

(ECG), non-invasive blood pressure (BP), heart rate (HR), pulse oxygen saturation (SpO2), invasive arterial pressure monitoring on radiologist arterial access line, arterial partial pressure of carbon dioxide (PaCO2), end-tidal carbon dioxide (ETCO2), inspired oxygen fraction (FiO2) and blood glucose. All patients will receive bispectral index (BIS) monitoring to assess the depth of sedation or anesthesia with BIS probe placed on the forehead. Physiologic parameters will be recorded using purposely designed data collection table. BP and blood glucose will be controlled according to current guidelines for stroke therapy [24-26]. Specifically, systolic blood pressure (SBP) is aimed to be kept between 140 and 180 mmHg and diastolic blood pressure (DBP) less than 105 mmHg, with vasopressor support if necessary. Plasma glucose will be maintained at level of 140-180 mg/dl while SPO2 is aimed to be over 94%, with FiO2 at a range from 40% to 60% [27]. It is anticipated that patients in the CS group may deteriorate during EVT and may, therefore, require endotracheal intubation or laryngeal mask insertion for airway protection[17]. All anesthesia related treatment will be performed by anesthesiologists of ischemia stroke team.

Interventions

GA and CS in this trial are defined according to the Practice guidelines for sedation and analgesia by non-anesthesiologists due to the continuum ranging of level of sedation from minimal sedation to GA[28]. Both GA and CS will be monitored and applied by anesthesiologist. In CS group, patients will receive sedative drugs and follow the sedation protocol as following: bolus propofol of 0.3-0.5 mg/kg, following continuous propofol infusion of 1-2 mg/kg/h and remifentanil infusion of 0.01-0.06 ug/kg/min. SpO_2 will be kept above 94% with 40%-60% inhaled oxygen at 3L/min flow and $ETCO_2$ is monitored via anesthetic gas sample line at nasal vestibule and kept normocapnia. The BIS value will be maintained above 70 via adjusting the infusion of sedative drugs.

In GA group, patients will receive rapid sequence induction with endotracheal

intubation or laryngeal mask insertion with propofol, remifentanil and muscle relaxant. Anesthesia will be induced with infusion of propofol of 1-2 mg/kg and remifentanil of 0.2-0.8 ug/kg for anesthesia induction[27]. Muscle relaxation will be achieved with rocuronium (0.6 mg/kg). After endotracheal intubation or laryngeal mask insertion, suction will be performed to mitigate risk of aspiration. Mechanical ventilation will be initiated to achieve normocapnia ($ETCO_2$ between 35 and 45 mmHg) with a 40%-60% fraction of inspired oxygen. Anesthesia will then be maintained with propofol (4-6 mg/kg/h) and remifentanil (0.05 to 0.1 ug/kg/min) infusion to maintain the BIS value between 40 and 60.

Converting from CS to GA is an important issue in this trial. In cases of procedural emergency including vessel perforation, intracranial hemorrhage (ICH), subarachnoid hemorrhage (SAH), seizures, deep coma, GCS decrease to or less than 8, respiratory failure ($ETCO_2 \geqslant 60$ mmHg, or $SpO_2<94\%$ without relevant improvement by increasing inhaled oxygen fraction) and severe disturbance of the treatment procedure (vomiting, substantial movement and uncoordinated dysphoria), CS will be converted to GA. The decision to convert from CS to GA will be made by the neuro-radiologist in charge and the attending anesthesiologist. The number of patients and reasons for the conversion will be recorded in detail. Criteria for converting from CS to GA is listed in Table 2.

Measurements

All patients will be regularly visited while in hospital by outcome assessors who are blinded to the treatment allocation. The incidence of complications, including myocardial infarction, non-fatal cardiac arrest, new stroke, pulmonary embolism and deep venous thrombosis will be recorded. All patients will receive brain imaging, including CTA, MRA before, 24 hours, 7 days (or at discharge, whichever sooner), 30 days and 90 days after randomization. Brain image will be used to assess new brain hemorrhage (if present) and infarct volume. Efficacy of vessels recanalization will be assessed by mTICI scale. The severity of stroke will be assessed using the NIHSS scale

during the same period. Disability will be rated at discharge and three months after EVT and rated using mRS. A glossary of measurements is shown in Supplementary file 2. To minimize loss of follow-up after discharge, study coordinators will contact the patients and his/her next-of-kin on a weekly basis. Besides, adverse effect will be also recorded.

Study objectives

The study aims to detect the difference of the post-procedural neurological function in patients with posterior circulation AIS under GA and CS, and hence to observe the effect of anesthesia type on outcomes after EVT.

Primary endpoint

The primary endpoint is the neurological disability at 90-day after EVT measured by mRS, which ranges from 0 (no symptoms) to 5 (severe disability), and a favorable neurological outcome is defined as no symptom or no significant disability with mRS $\leqslant 2$[3 15 29 30]. The score will be evaluated by outcomes assessor who are blinded to allocation.

Secondary endpoints

The secondary endpoints include the followings:

1. Change in NIHSS, from baseline to 24 h, 7 days (or at discharge), 30 days and 3 months after randomization.
2. The score of mTICI will be evaluated before and after endovascular treatment.
3. All-cause mortality up to 3 months after randomization.
4. The incidence of complications up to 3 months after randomization.
5. The length of stay in the hospital and in intensive care unit after randomization.
6. The rate of conversion from CS to GA.
7. Work-flow time, including door to door, door to groin puncture, puncture complete, groin puncture to recanalization and treatment time.
8. All adverse events associated with this study will be recorded.

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. The DMC are responsible for terminating the research in case of severe adverse events.

Statistical analysis plan

Descriptive statistics will be reported as means with standard deviation and medians with interquartile range for normally distributed data and skewed continuous data, respectively, and counts (percentage) for categorical data. The data will be analyzed on intention to treat and per protocol, however, the conclusion will be drawn according to the intention-to-treat analysis. The intention-to-treat analysis will depend on the allocated population while the per-protocol analysis will depend on the actual anesthesia method the population receive. Differences in the primary endpoint will be compared between groups using Cochran-Mantel-Haenszel test. Furthermore, primary outcome will be analyzed in following subgroups: age, gender, baseline NIHSS score; time from onset of stroke to EVT, site of arterial occlusion, and mTICI score. Other categorical variables will be analyzed by χ^2 test and continuous variables using Student-t test or Mann-Whitney U test.

To allow for a varying number of follow-up measurements, the repeated measure ANOVA methods with a mixed model approach (treating time as a random effect and other covariates as fixed effects) will be utilized, and the specific comparison of change in each of those measurements between baseline and any specific post-baseline time point can be tested using linear contrast. In addition, missing data will be imputed using inverse probability weighting and the worst-case imputation scenarios. STATA 14.0 (StataCorp LP, College Station, TX) for windows will be used for all statistical analyses. The statistical significance will be declared at type I error of 0.05.

Sample size calculation

The PASS 15 software (NCSS, LLC, USA) is used to calculate the sample size based

on the primary endpoint – favorable outcome (mRS 0-2) at three months after randomization. Several trials focused on the neurological outcome of patients with posterior circulation AIS, however, only two indicated the association between anesthesia type and neurological outcome. In the case-control study of Ashutosh et al, they reported the incidence of mRS≤2 at 90-day was 38.3% in CS and 31.1% in GA[21]. On the other hand, a retrospective observational study in our institution reported a higher incidence of favorable neurological outcome at 90-day in CS compared to GA group (68.7% vs 35.6%)[31]. However, other factors including pre-operative NIHSS score, pre-operative intravenous thrombolysis treatment confound the results validity[31]. Meanwhile, in previous anterior circulation research, AIS patients receiving GA presented a favorable or similar neurological outcome at 90 days compared with CS[13 19 32]. Taking this into account, we consider that the sample size to detect 30% difference in mRS 0-2 would require 44 in each group to achieve power of 80% at a two-tailed significant level of 0.05, with a drop-out rate of 5%[33].

Reporting of adverse events

All adverse events associated with this trial will be recorded and closely monitored until resolution or stabilization or until it has been shown that study treatment is not the cause of the event. The principal investigator is responsible for reporting all adverse events. Once adverse events occur, it should be immediately reported to the research department and informed to the principal investigator to determine the severity of the adverse events. All adverse events associated with this study will be recorded and reported to the Ethics Committee within 24 hours.

Protocol Amendment

The chief investigator will be responsible for any decision to amend the protocol. If there is any modification (eg, changes to eligibility criteria, outcomes, analyses) the principle investigator will communicate and gain approval from the Ethical Committee of Beijing Tiantan Hospital, Capital Medical University prior to implementation, and communicate with relevant parties.

Ethics and dissemination

The approval for the study was certificated by the Ethical Committee of Beijing Tiantan Hospital, Capital Medical University on 19 December, 2017 (reference number: KY2017- 074-02). The study was registered on clincaltrials.gov on 23 October, 2017 (NCT03317535). The study recruited the first patient on 1 February, 2018, and the estimated study completion date will be 31 Dec, 2020.The findings of the study will be published in peer-reviewed journals and will be presented at national or international conferences.

DISCUSSION

This is an exploratory controlled randomized study aiming to detect the effect of anesthesia choice on the neurological outcome in the patients with posterior circulation AIS undergoing EVT. The study aims to test the hypothesis that GA and CS have different effects on the post-endovascular procedure neurological outcomes in patients with posterior circulation AIS.

Anesthetic selection and peri-procedural management could be associated with outcomes in patients with posterior circulation AIS undergoing EVT. The hemodynamics disturbance and the changes in carbon dioxide tension may be associated with the outcomes. However, no consistent agreement about the anesthesia modality has been reached, the anesthetic protocols vary among different stroke centers. In daily clinical work, the actual practice of anesthesia for EVT, especially for posterior circulation AIS patients, largely rely on local protocols and individual preference of neuro-radiologists or anesthesiologists. CS may be used for cooperative patients and GA for severely agitated, non-conscious and unprotected airway patients[13]. A small number of retrospective studies (including patients with posterior circulation AIS) show that CS groups have better clinical outcomes, lower complication rate, shorter reperfusion time and less changes in hemodynamics and respiration[21 22 31]. In contrary, GA groups could suffer from worse neurological function, lower blood pressure, aspiration pneumonia and/or high mortality [34-41]. A recent retrospective, matched, case-

control study of patients with posterior circulation AIS is the only study to explore the effect of anesthesia management on outcome of patients with posterior AIS, however, great limitation and drawbacks in terms of study design, including selection bias and information bias impede the credibility of the results[21]. Several confounding factors contribute to inconclusive results, including specific information of peri-interventional management, such as blood pressure, partial pressure of carbon dioxide, and strict uniform anesthesia protocol. Therefore, a prospective, randomized, controlled trial is required to account for the peri-procedural confounders and demonstrate the effects of anesthesia (type and management) on outcomes for patients with posterior AIS undergoing EVT.

This trial aims to explore the effect of anesthesia choice on the post-endovascular procedure outcomes in patients with posterior circulation AIS using a randomized controlled trial design. The features of the current study involve strict randomized system, clear inclusion and exclusion criteria, a rigorous uniform protocol to manage hemodynamic, respiratory parameters and blood glucose in GA and CS group, and full-time attending anesthesiologists in each procedure. The findings of the study would contribute to serve as a reference for a future multi-center trial to verify the effects of anesthesia on patients with posterior circulation AIS undergoing EVT.

Patient and public involvement

Patients and the public were not directly consulted in the development of the research question or outcome measures. Patients were not involved in the design, the recruitment and conduct of the study. At the completion of this trial, a manuscript will be prepared to present the trial results. Results of the final study will be disseminated to all study participants through their preferred method of communication indicated at the time of enrollment.

Competing interests

None declared.

Funding

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Author contributions

FL and YZ conceived the study. FL, YZ, SL, ZM, YP and RH initiated the study design and helped with protocol development and implementation. FL, YX, YW, YZ and MJ helped in data collection and manuscript revision. YP and RH are the grant holders. FL and YZ are the co-first authors. YP is the responsible author. All authors contributed to refinement of the study protocol. All authors have read and approved the final manuscript.

Ethics approval

This study is approved by the Ethical Committee of Beijing Tiantan Hospital, Capital Medical University (reference number: KY2017- 074-02).

Data sharing statement

This manuscript is a protocol for a randomized controlled trial, which does not include data.

List of tables and figures:

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Table 2. Criteria for converting from conscious sedation to general anesthesia

Figure 1. CONSORT flow diagram for CANVAS II clinical trial.

Supplementary file 1 SPIRIT checklist.

Supplementary file 2 Measurement glossary.

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Table 1. Schedule of enrollment, intervention and assessment.

	STUDY PERIOD							
	Enrolment	**Allocation**	**Post-allocation**					
TIMEPOINT	***At arrival***	**After evaluation**	***During treatment***	***24h after treatment***	***7 days after treatment***	***Discharge***	***30 days after treatment***	***90 days after treatment***
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
INTERVENTIONS:								
GA			X					
CS			X					
ASSESSMENTS:								
Baseline variables	X	X						
Brain image	X			X				
mRS							X	X
NIHSS	X			X	X		X	X
mTICI			X					
All-cause mortality								X
length of stay								X
ICU stay and length								X
Converting rate			X					
Adverse event			X					X

GA: general anesthesia; CS: conscious sedation; NIHSS: National Institute of Health Stroke Scale;

mRS: modified Rankin Score; mTICI: modified Thrombolysis in Cerebral Infarction Scale

Table 2 Criteria for converting from conscious sedation to general anesthesia.

1. Unconscious;
2. GCS decrease to or less than 8;
3. Increase of ETCO2 ≥60 mmHg and/or a decrease in S_PO_2<94% despite oxygen supplementation;
4. Agitation that cannot be controlled with sedation and/or restraint;
5 Seizure attack;
6. Vomiting;
7. Recognized complications from endovascular therapy, such as vessel perforation leading to intracerebral hemorrhage or subarachnoid hemorrhage.

GCS: Glascow coma scale; S_PO_2: pulse oxygen saturation; $ETCO_2$: end-tidal carbon dioxide.

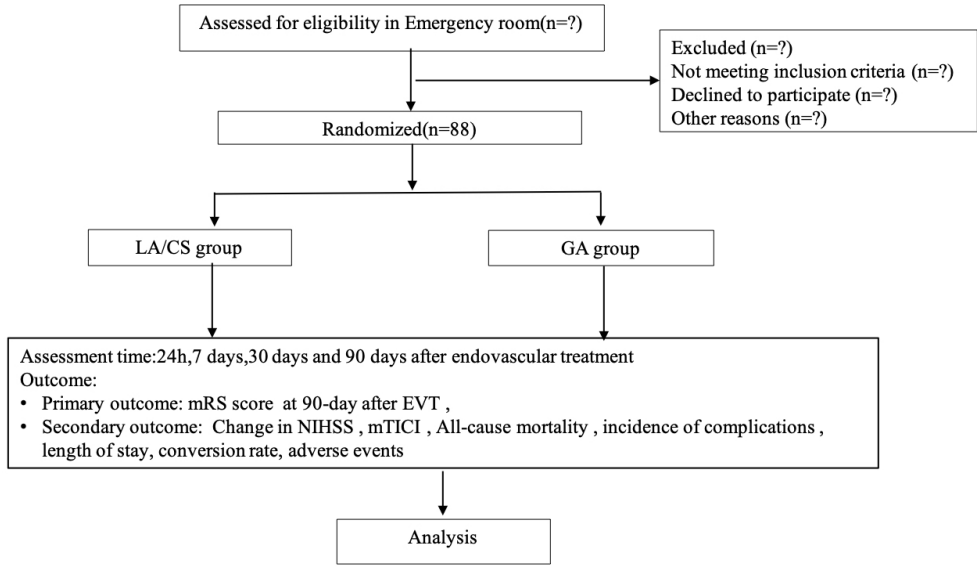

Figure 1. CONSORT flow diagram for CANVAS II clinical trial.

Figure 1. CONSORT flow diagram for CANVAS II clinical trial.

216x142mm (150 x 150 DPI)

Supplementary file 1: SPIRIT checklist.

Section/item	ItemNo	Description	page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1,7
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,15
	5b	Name and contact information for the trial sponsor	1,15

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5-6
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8,11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10, Table 1
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	NA
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Yes
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

Supplementary file 2 Measurement glossary

Physiological parameters		
Acronyms	**Full Names**	**Definition and Measurement description**
SBP	systolic blood pressure	Recorded 10 min before treatment and every 10min during procedure in case report form (CRF) table, every 5min in electronic medical record system. Target value:>140mmHg, <180mmHg.
DBP	diastolic blood pressure	Recorded 10 min before treatment and every 10min during procedure in CRF table, every 5min in electronic medical record system. Target value:>105mmHg
FiO_2	inspired oxygen fraction	Recorded 10 min before treatment and every 10min during procedure in CRF table, every 5min in electronic medical record system.
$PaCO_2$	arterial partial pressure of carbon dioxide	Tested through arterial line access. Tested every 1 hour during endovascular therapy (EVT).
$ETCO_2$	end-tidal carbon dioxide	Recorded 10 min before treatment and every 10min during procedure in CRF table, every 5min in electronic medical record system.
BIS	bispectral index	Recorded 10 min before treatment and every 10min during procedure in CRF table, every 5min in electronic medical record system.
ECG	electrocardiography	Recorded 5min in electronic medical record system.
HR	heart rate	Recorded 10 min before treatment and every 10min during procedure in CRF table, every 5min in electronic medical record system.

SpO_2	pulse oxygen saturation	Recorded 10 min before treatment and every 10min during procedure in CRF table, every 5min in electronic medical record system.
BP	blood pressure	Non-invasive blood pressure on either arm, measured every 5min during procedure. Recorded 10 min before treatment and every 10min during procedure in CRF table, every 5min in electronic medical record system.
Glu	serum glucose	Tested before EVT treatment. During EVT, tested every 1 hour. Target value: 70-140mg/L
MAP	mean artery pressure	Recorded 10 min before treatment and every 10min during procedure in CRF table, every 5min in electronic medical record system.
ABG	arterial blood gas	Monitored before treatment and every one hour during treatment, including Na+, K_+, Cl_-, PaCO2, PaO2, PH, glucose.
Evaluation		
Acronyms	**Full Names**	**Definition and Measurement description**
mRS	modified Rankin scale	Measured before treatment, 24h and 90 days after treatment
NIHSS	National Institute of Health stroke scale	Measured before treatment, 24h and 90 days after treatment
mTIMI	modified Thrombolysis in Myocardial Infarction	Measured before EVT and immediately after recanalization.
GCS	Glasgow coma score	Measured before treatment, 24h and 90 days after treatment
pc-ASPECTS	post-circulation Alberta Stroke Program Early CT Score	Measured before treatment
Work flow		

Name	Definition and description
Onset to door	The duration between patient last know to be well and arriving to radiological suite.
Door to groin puncture	The duration between patient arriving at radiological suite and groin puncture initiating.
Puncture complete	The duration between groin puncture initiating and puncture completing.
Groin puncture to recanalization	The time duration between puncture complete and recanalization.
Recanalization time	The time duration between onset to recanalization success.
Recover time	The time duration between pressing against the puncture site and transferring to NICU.

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Choice of ANesthesia for EndoVAScular Treatment of Acute Ischemic Stroke at Posterior Circulation (CANVAS II): Protocol for an Exploratory Randomized Controlled Study

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Choice of ANesthesia for EndoVAScular Treatment of Acute Ischemic Stroke at Posterior Circulation (CANVAS II): Protocol for an Exploratory Randomized Controlled Study

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ABSTRACT

Introduction

Observational and interventional studies indicate that the type of anesthesia may be associated with the post-procedural neurological function in patients with anterior circulation acute ischemic stroke undergoing endovascular treatment. Patients with acute posterior circulation ischemic stroke may experience different physiological changes and result in severe neurological outcome. However, the effect of the type of anesthesia on post-procedure neurological function remained unclear in this population.

Methods and analysis

This is an exploratory randomized controlled trial that will be carried out at Beijing Tiantan Hospital, Capital Medical University. Patients with acute posterior circulation ischemic stroke and deemed suitable for emergency endovascular recanalization will be recruited in this trial. Eighty-four patients will be randomized to receive either general anesthesia or conscious sedation with 1:1 allocation ratio. The primary endpoint is the 90-day modified Rankin Scale.

Ethics and dissemination

The study is registered at the ClinicalTrial.gov (NCT03317535) and has been reviewed by and approved by Ethics Committee of Beijing Tiantan Hospital of Capital Medical University (KY2017-074-02). If the results are positive, the study will indicate whether the type of anesthesia affects neurological outcome after endovascular treatment of posterior stroke. The findings of the study will be published in peer-reviewed journals and presented at national or international conferences.

Trial registration number: NCT03317535

Keywords

General anesthesia, Conscious sedation, Endovascular treatment, Posterior circulation, Acute ischemic stroke, Neurological outcome

Article Summary

Strengths and limitations of this study

- This is the first randomized control study to observe the effect of anesthesia modality on neurological outcome of patients with posterior circulation acute ischemic stroke.
- This study involves strict randomized system, clear inclusion and exclusion criteria, a rigorous uniform protocol to balance intraoperative variables between groups.
- One limitation of the study is it is a single-centered trial, future multicenter trial is needed to verify the effects of anesthesia on patients with posterior circulation acute ischemic stroke undergoing endovascular treatment.
- The sample size is relatively small and the result will need to be confirmed by larger-size trials.
- Patients are selected mainly based on time window, salvageable ischemic brain tissue and initial infarct size might be considered in the inclusion criteria.

INTRODUCTION

Acute ischemic stroke (AIS) at posterior circulation account for 17%-60% of acute ischemic stroke with difficulty in treatment, which result in a poor outcome and mortality rate of 80%-95%[1-5]. Early recanalization is one of the most important predictors of favorable outcome for posterior circulation AIS patients at 90 days [6]. Though endovascular therapy (EVT) has been demonstrated to be an effective and safe treatment with around 30% good clinical outcome improvement and 35% mortality decrease at 90 days, there is a substantial proportion of patients with poor clinical outcomes even after timely successful reperfusion[7-10]. Many factors may contribute to the mismatched association of high reperfusion rate and poor clinical outcome, including patient-specific factors (age, collaterals status, initial stroke severity, infarct volume and site, and distal artery emboli, etc.), procedural-specific factors (time from onset to recanalization, degree of recanalization) and anesthesia management[2 11 12].

The optimal anesthesia choice and management for AIS patients during EVT, general anesthesia (GA) or conscious sedation (CS), is still unclear. Benefits of GA with tracheal intubation or laryngeal mask include secured airway to avoid aspiration, body immobility to avoid vessel perforation and better digital subtraction angiography imaging. On the other hand, hypotension, nosocomial infection, delayed procedure initiation, loss of neurological evaluation, and hyperventilation may contribute to poor outcomes. CS management permits neurological function assessment, shortens mean time from door to groin puncture and minimizes hemodynamic changes associate with GA. However, the risk of aspiration and substantial movement during endovascular procedural are the main two disadvantages associated with CS [13-17].

Three randomized controlled trials have compared the neurological outcomes after EVT with GA or CS in anterior circulation. The Sedation vs. Intubation for Endovascular Stroke TreAtment (SIESTA) trial reported similar National Institute of Health stroke scale (NIHSS) scores at 24 hours between GA and CS, but favorable outcomes, measured by modified Rankin scale (mRS) was found in patients with GA 3

months after treatment as a secondary outcome measure[14]. Similarly, the General Or Local anesthesia in Intra Arterial THerapy (GOLIATH) trial reported similar brain infarct volume and favorable 90-day mRS score increased with GA[18]. However, The Anesthesia during Stroke (AnStroke) trial reported no difference between GA and CS in 90-day mRS[19]. Recently, a meta-analysis using fixed-effects model by obtaining individual patient data from the above-3 trials with blinded endpoint evaluation, indicated significantly different results in favor of the GA group (cOR=1.58, 95% CI 1.09-2.29)[20]. Nevertheless, these findings should be interpreted with caution. Firstly, these trials only provided insight into choice of anesthesia modality in the anterior circulation AIS population, the result of above researches are not appropriate for patients with posterior circulation occlusions. Secondly, only AnStroke trial analyzed the neurological function at 90 days as the primary outcome, while in other 2 trials, it was analyzed as a secondary outcome. Hence the conclusion on relationship between anesthesia and neurological function at 90 days should be drawn with caution [19].

A few studies observed the feasibility of monitored anesthesia care for elective endovascular procedures either in anterior or posterior circulations, and demonstrated high technical success with low rates of peri-procedural complications and mortality[21] [22]. Although these studies included a relatively large proportion of posterior circulation interventions and showed promising results about feasibility of monitored anesthesia care, it is unreasonable to employ previous results in emergent setting, with potential presence of severe midbrain ischemia. Moreover, only one study focused purely on the posterior circulation patients and investigated the influence of anesthesia modality and management on clinical and angiographic outcomes[21]. In this retrospective, matched, case-control study, CS was found to be feasible and appeared to be as safe and effective as GA. However, retrospective design and relatively limited sample size may introduce undetected biases. Furthermore, there is no published randomized controlled trial that explored whether GA or CS are associated with different neurological outcome at 90 days in patients undergoing EVT for posterior circulation AIS.

On the basis of previous studies, we propose to conduct a trial to compare neurological outcome in posterior circulation AIS patients receiving GA with those receiving CS for EVT.

METHODS

The protocol has been prepared according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[23]. All trial procedures are summarized in Table 1. For completed checklists, see Supplementary file 1.

Study design

This is a randomized, parallel-group, exploratory trial with blinded endpoint evaluation to determine whether GA or CS produces different neurological outcomes in posterior circulation AIS patients undergoing EVT. Posterior circulation AIS patients will be enrolled from Beijing Tiantan Hospital, Capital Medical University from 2018 to 2020. This trial was approved by the Ethics Committee of Beijing Tiantan Hospital of Capital Medical University (KY2017-074-02) and registered in www.clincaltrials.gov (NCT03317535). The participants flowchart is briefly illustrated in Figure 1

Participants

Posterior circulation AIS Patients who deemed suitable for recanalization of the culprit's vessels will be considered for recruitment in the study. The inclusion criteria are vertebral artery and/or basilar artery responsible for posterior circulation ischemia confirmed by computed tomography angiography (CTA)/ magnetic resonance angiography (MRA), the modified Thrombolysis in Cerebral Infarction (mTICI) score ≤1, age ≥18 years, stroke onset to treatment time ≤ 24 hours, and modified Rankin Score≤2 before onset.

Patients with unclear radiological image to identify infarction and vessel occlusion, with intracranial hemorrhage, anterior circulation occlusion, Glasgow coma score （GCS） ≤8, NIHSS score < 6 or > 30, post-circulation Alberta Stroke Program Early CT Score (pc-ASPECTS) < 6, pons-midbrain index ≥ 3, severe agitation or seizures,

loss of airway protective reflexes and/or vomiting on admission, intubated before EVT, unconsciousness, and known allergy to anesthetics or analgesics will be excluded from the study. Patient whose legal relative refuses to participate will be excluded. Both the neuro-radiologists and the attending anesthesiologist must agree that the patient is suitable with either GA or CS management before recruiting. Reasons why eligible patients are not recruited to the trial will be documented.

Randomization and blinding

Randomization occurs on the time of EVT when patients are admitted to the interventional neuroradiology suite, the decision for EVT has been made, and written informed consent (Supplementary file 2) is obtained from patient's legal representatives. Randomization will be conducted via a computer-generated table. Patients will be randomly allocated to receive either GA or CS in a 1 to 1 ratio. A designated staff who will neither be involved in anesthesia management nor follow-up will perform recruitment as well as allocation randomization sequence. This designated staff will implement the allocation sequence through opaque, sealed and stapled envelopes. The endpoint assessors will be blinded to the randomization group.

Standard operating procedures are applied to both groups to ensure no principal differences generated and uniform protocol implemented. Patients in both groups will receive local anesthesia at puncture site, with 3-5 ml of 1% lidocaine hydrochloride prior to arterial puncture. The outcome assessors are blinded to the information of treatment for the enrolled patients and will evaluate the outcome variables for this study to ensure unbiased reporting. The anesthesiologist, neuro-radiologist as well as attending doctors in neurological intensive care unit (NICU) will not be blinded as they need to participate in the safe administration of GA or CS and related medical care. The enrolled patients and his/her legal representatives will not be blinded, either.

Standard anesthesia management protocols during EVT (Concomitant treatment)

All randomized patients will receive standard monitoring, including electrocardiography (ECG), non-invasive blood pressure (BP), heart rate (HR), pulse oxygen saturation (SpO2), invasive arterial pressure monitoring on radiologist arterial access line, arterial partial pressure of carbon dioxide (PaCO2), end-tidal carbon dioxide (ETCO2), inspired oxygen fraction (FiO2) and blood glucose. All patients will receive bispectral index (BIS) monitoring to assess the depth of sedation or anesthesia with BIS probe placed on the forehead. Physiologic parameters will be recorded using purposely designed data collection table. BP and blood glucose will be controlled according to current guidelines for stroke therapy [24-26]. Specifically, systolic blood pressure (SBP) is aimed to be kept between 140 and 180 mmHg and diastolic blood pressure (DBP) less than 105 mmHg, with vasopressor support if necessary. Plasma glucose will be maintained at level of 140-180 mg/dl while SPO2 is aimed to be over 94%, with FiO2 at a range from 40% to 60% [27]. It is anticipated that patients in the CS group may deteriorate during EVT and may, therefore, require endotracheal intubation or laryngeal mask insertion for airway protection[17]. All anesthesia related treatment will be performed by anesthesiologists of ischemia stroke team.

Interventions

GA and CS in this trial are defined according to the Practice guidelines for sedation and analgesia by non-anesthesiologists due to the continuum ranging of level of sedation from minimal sedation to GA[28]. Both GA and CS will be monitored and applied by anesthesiologist. In CS group, patients will receive sedative drugs and follow the sedation protocol as following: bolus propofol of 0.3-0.5 mg/kg, following continuous propofol infusion of 1-2 mg/kg/h and remifentanil infusion of 0.01-0.06 ug/kg/min. SpO_2 will be kept above 94% with 40%-60% inhaled oxygen at 3L/min flow and $ETCO_2$ is monitored via anesthetic gas sample line at nasal vestibule and kept normocapnia. The BIS value will be maintained above 70 via adjusting the infusion of sedative drugs.

In GA group, patients will receive rapid sequence induction with endotracheal intubation or laryngeal mask insertion with propofol, remifentanil and muscle relaxant. Anesthesia will be induced with infusion of propofol of 1-2 mg/kg and remifentanil of 0.2-0.8 ug/kg for anesthesia induction[27]. Muscle relaxation will be achieved with rocuronium (0.6 mg/kg). After endotracheal intubation or laryngeal mask insertion, suction will be performed to mitigate risk of aspiration. Mechanical ventilation will be initiated to achieve normocapnia ($ETCO_2$ between 35 and 45 mmHg) with a 40%-60% fraction of inspired oxygen. Anesthesia will then be maintained with propofol (4-6 mg/kg/h) and remifentanil (0.05 to 0.1 ug/kg/min) infusion to maintain the BIS value between 40 and 60.

Converting from CS to GA is an important issue in this trial. In cases of procedural emergency including vessel perforation, intracranial hemorrhage (ICH), subarachnoid hemorrhage (SAH), seizures, deep coma, GCS decrease to or less than 8, respiratory failure ($ETCO_2 \geq 60$ mmHg, or $SpO_2 < 94\%$ without relevant improvement by increasing inhaled oxygen fraction) and severe disturbance of the treatment procedure (vomiting, substantial movement and uncoordinated dysphoria), CS will be converted to GA. The decision to convert from CS to GA will be made by the neuro-radiologist in charge and the attending anesthesiologist. The number of patients and reasons for the conversion will be recorded in detail. Criteria for converting from CS to GA is listed in Table 2.

Measurements

All patients will be regularly visited while in hospital by outcome assessors who are blinded to the treatment allocation. The incidence of complications, including myocardial infarction, non-fatal cardiac arrest, new stroke, pulmonary embolism and deep venous thrombosis will be recorded. All patients will receive brain imaging, including CTA, MRA before, 24 hours, 7 days (or at discharge, whichever sooner), 30 days and 90 days after randomization. Brain image will be used to assess new brain hemorrhage (if present) and infarct volume. Efficacy of vessels recanalization will be assessed by mTICI scale. The severity of stroke will be assessed using the NIHSS scale

during the same period. Disability will be rated at discharge and three months after EVT and rated using mRS. A glossary of measurements is shown in Supplementary file 3. To minimize loss of follow-up after discharge, study coordinators will contact the patients and his/her next-of-kin on a weekly basis. Besides, adverse effect will be also recorded.

Study objectives

The study aims to detect the difference of the post-procedural neurological function in patients with posterior circulation AIS under GA and CS, and hence to observe the effect of anesthesia type on outcomes after EVT.

Primary endpoint

The primary endpoint is the neurological disability at 90-day after EVT measured by mRS, which ranges from 0 (no symptoms) to 5 (severe disability), and a favorable neurological outcome is defined as no symptom or no significant disability with mRS≤ 2[3 15 29 30]. The score will be evaluated by outcomes assessor who are blinded to allocation.

Secondary endpoints

The secondary endpoints include the followings:

1. Change in NIHSS, from baseline to 24 h, 7 days (or at discharge), 30 days and 3 months after randomization.
2. The score of mTICI will be evaluated before and after endovascular treatment.
3. All-cause mortality up to 3 months after randomization.
4. The incidence of complications up to 3 months after randomization.
5. The length of stay in the hospital and in intensive care unit after randomization.
6. The rate of conversion from CS to GA.
7. Work-flow time, including door to door, door to groin puncture, puncture complete, groin puncture to recanalization and treatment time.
8. All adverse events associated with this study will be recorded.

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. The DMC are responsible for terminating the research in case of severe adverse events.

Statistical analysis plan

Descriptive statistics will be reported as means with standard deviation and medians with interquartile range for normally distributed data and skewed continuous data, respectively, and counts (percentage) for categorical data. The data will be analyzed on intention to treat and per protocol, however, the conclusion will be drawn according to the intention-to-treat analysis. The intention-to-treat analysis will depend on the allocated population while the per-protocol analysis will depend on the actual anesthesia method the population receive. Differences in the primary endpoint will be compared between groups using Cochran-Mantel-Haenszel test. Furthermore, primary outcome will be analyzed in following subgroups: age, gender, baseline NIHSS score; time from onset of stroke to EVT, site of arterial occlusion, and mTICI score. Other categorical variables will be analyzed by χ^2 test and continuous variables using Student-t test or Mann-Whitney U test.

To allow for a varying number of follow-up measurements, the repeated measure ANOVA methods with a mixed model approach (treating time as a random effect and other covariates as fixed effects) will be utilized, and the specific comparison of change in each of those measurements between baseline and any specific post-baseline time point can be tested using linear contrast. In addition, missing data will be imputed using inverse probability weighting and the worst-case imputation scenarios. STATA 14.0 (StataCorp LP, College Station, TX) for windows will be used for all statistical analyses. The statistical significance will be declared at type I error of 0.05.

Sample size calculation

The PASS 15 software (NCSS, LLC, USA) is used to calculate the sample size based on the primary endpoint – favorable outcome (mRS 0-2) at three months after randomization. Several trials focused on the neurological outcome of patients with posterior circulation AIS, however, only two indicated the association between anesthesia type and neurological outcome. In the case-control study of Ashutosh et al, they reported the incidence of mRS≤2 at 90-day was 38.3% in CS and 31.1% in GA[21]. On the other hand, a retrospective observational study in our institution reported a higher incidence of favorable neurological outcome at 90-day in CS compared to GA group (68.7% vs 35.6%)[31]. However, other factors including pre-operative NIHSS score, pre-operative intravenous thrombolysis treatment confound the results validity[31]. Meanwhile, in previous anterior circulation research, AIS patients receiving GA presented a favorable or similar neurological outcome at 90 days compared with CS[13 19 32]. Taking this into account, we consider that the sample size to detect 30% difference in mRS 0-2 would require 44 in each group to achieve power of 80% at a two-tailed significant level of 0.05, with a drop-out rate of 5%[33].

Reporting of adverse events

All adverse events associated with this trial will be recorded and closely monitored until resolution or stabilization or until it has been shown that study treatment is not the cause of the event. The principal investigator is responsible for reporting all adverse events. Once adverse events occur, it should be immediately reported to the research department and informed to the principal investigator to determine the severity of the adverse events. All adverse events associated with this study will be recorded and reported to the Ethics Committee within 24 hours.

Protocol Amendment

The chief investigator will be responsible for any decision to amend the protocol. If there is any modification (eg, changes to eligibility criteria, outcomes, analyses) the principle investigator will communicate and gain approval from the Ethical Committee

of Beijing Tiantan Hospital, Capital Medical University prior to implementation, and communicate with relevant parties.

Ethics and dissemination

The approval for the study was certificated by the Ethical Committee of Beijing Tiantan Hospital, Capital Medical University on 19 December, 2017 (reference number: KY2017- 074-02). The study was registered on clincaltrials.gov on 23 October, 2017 (NCT03317535). The study recruited the first patient on 1 February, 2018, and the estimated study completion date will be 31 Dec, 2020.The findings of the study will be published in peer-reviewed journals and will be presented at national or international conferences.

DISCUSSION

This is an exploratory controlled randomized study aiming to detect the effect of anesthesia choice on the neurological outcome in the patients with posterior circulation AIS undergoing EVT. The study aims to test the hypothesis that GA and CS have different effects on the post-endovascular procedure neurological outcomes in patients with posterior circulation AIS.

Anesthetic selection and peri-procedural management could be associated with outcomes in patients with posterior circulation AIS undergoing EVT. The hemodynamics disturbance and the changes in carbon dioxide tension may be associated with the outcomes. However, no consistent agreement about the anesthesia modality has been reached, the anesthetic protocols vary among different stroke centers. In daily clinical work, the actual practice of anesthesia for EVT, especially for posterior circulation AIS patients, largely rely on local protocols and individual preference of neuro-radiologists or anesthesiologists. CS may be used for cooperative patients and GA for severely agitated, non-conscious and unprotected airway patients[13]. A small number of retrospective studies (including patients with posterior circulation AIS) show that CS groups have better clinical outcomes, lower complication rate, shorter reperfusion time and less changes in hemodynamics and respiration[21 22 31]. In contrary,

GA groups could suffer from worse neurological function, lower blood pressure, aspiration pneumonia and/or high mortality [34-41]. A recent retrospective, matched, case-control study of patients with posterior circulation AIS is the only study to explore the effect of anesthesia management on outcome of patients with posterior AIS, however, great limitation and drawbacks in terms of study design, including selection bias and information bias impede the credibility of the results[21]. Several confounding factors contribute to inconclusive results, including specific information of peri-interventional management, such as blood pressure, partial pressure of carbon dioxide, and strict uniform anesthesia protocol. Therefore, a prospective, randomized, controlled trial is required to account for the peri-procedural confounders and demonstrate the effects of anesthesia (type and management) on outcomes for patients with posterior AIS undergoing EVT.

This trial aims to explore the effect of anesthesia choice on the post-endovascular procedure outcomes in patients with posterior circulation AIS using a randomized controlled trial design. The features of the current study involve strict randomized system, clear inclusion and exclusion criteria, a rigorous uniform protocol to manage hemodynamic, respiratory parameters and blood glucose in GA and CS group, and full-time attending anesthesiologists in each procedure. The findings of the study would contribute to serve as a reference for a future multi-center trial to verify the effects of anesthesia on patients with posterior circulation AIS undergoing EVT.

Patient and public involvement

Patients and the public were not directly consulted in the development of the research question or outcome measures. Patients were not involved in the design, the recruitment and conduct of the study. At the completion of this trial, a manuscript will be prepared to present the trial results. Results of the final study will be disseminated to all study participants through their preferred method of communication indicated at the time of enrollment.

Competing interests

None declared.

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Author contributions

FL and Yan Zhao conceived the study. FL, YZ, SL, ZM, YP and RH initiated the study design and helped with protocol development and implementation. FL, XY, XL YW, Yang Zhou and MJ helped in data collection and manuscript revision. YP and RH are the grant holders. FL and Yan Zhao are the co-first authors. YP is the responsible author. All authors contributed to refinement of the study protocol. All authors have read and approved the final manuscript.

Ethics approval

This study is approved by the Ethical Committee of Beijing Tiantan Hospital, Capital Medical University (reference number: KY2017- 074-02).

Data sharing statement

This manuscript is a protocol for a randomized controlled trial, which does not include data.

List of tables and figures:

Table 1. Schedule of enrollment, intervention and assessment.

Table 2. Criteria for converting from conscious sedation to general anesthesia

Figure 1. CONSORT flow diagram for CANVAS II clinical trial.

Supplementary file 1 SPIRIT checklist.

Supplementary file 2 Informed consent

Supplementary file 3 Measurement glossary.

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Table 1. Schedule of enrollment, intervention and assessment.

	STUDY PERIOD							
	Enrolment	**Allocation**	**Post-allocation**					
TIMEPOINT	***At arrival***	**After evaluation**	***During treatment***	***24h after treatment***	***7 days after treatment***	***Discharge***	***30 days after treatment***	***90 days after treatment***
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
INTERVENTIONS:								
GA			X					
CS			X					
ASSESSMENTS:								
Baseline variables	X	X						
Brain image	X			X				
mRS							X	X
NIHSS	X			X	X		X	X
mTICI			X					
All-cause mortality								X
length of stay								X
ICU stay and length								X
Converting rate			X					
Adverse event			X					X

GA: general anesthesia; CS: conscious sedation; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin Score; mTICI: modified Thrombolysis in Cerebral Infarction Scale

Table 2 Criteria for converting from conscious sedation to general anesthesia.

1. Unconscious;
2. GCS decrease to or less than 8;
3. Increase of ETCO2 ≥60 mmHg and/or a decrease in S_PO_2<94% despite oxygen supplementation;
4. Agitation that cannot be controlled with sedation and/or restraint;
5 Seizure attack;
6. Vomiting;
7. Recognized complications from endovascular therapy, such as vessel perforation leading to intracerebral hemorrhage or subarachnoid hemorrhage.

GCS: Glascow coma scale; $S_PO_{2:}$ pulse oxygen saturation; $ETCO_{2;}$ end-tidal carbon dioxide.

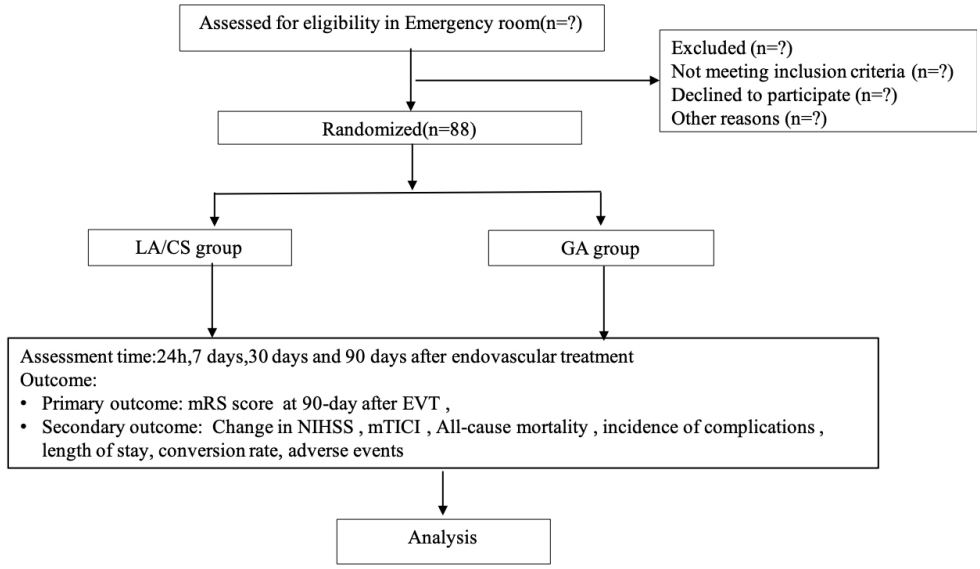

Figure 1. CONSORT flow diagram for CANVAS II clinical trial.

Figure 1. CONSORT flow diagram for CANVAS II clinical trial.

216x142mm (150 x 150 DPI)

Supplementary file 1: SPIRIT checklist.

Section/item	ItemNo	Description	page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1,7
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,15
	5b	Name and contact information for the trial sponsor	1,15

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5-6
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8,11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10, Table 1
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	NA
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Yes
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

Supplementary file 2

INFORMED CONSENT

Choice of ANesthesia for EndoVAScular Treatment of Acute Ischemic Stroke at Posterior Circulation (CANVAS II)

Project entrust organization：Beijing Tian Tan Hospital, CMU

Contract Research Organization：N/A

Version：1.3

28th, Dec, 2017

INFORMATION SHEET

You have been diagnosed with ***acute ischemic stroke in posterior circulation*** and you will receive emergency endovascular treatment.

We would like to invite you to participate our study, which is "***Choice of ANesthesia for EndoVAScular Treatment of Acute Ischemic Stroke at Posterior Circulation*** ",to observe the effect of general anesthesia and conscious sedation on clinical outcome. This study is approved by Ethics Committee of Beijing Tiantan Hospital of Capital Medical University.During our study, we will follow the Declaration of Helsinki.

Before you decide whether participate this clinical trial, please take time to review this information carefully. This form describes the purpose, procedure, study duration, risks and possible benefits of participating the study. You may also wish to talk to others, including your friends, family, or discuss with your anesthesiologist, about your participation in this study.

1. PURPOSE of THIS STUDY

In China, cerebrovascular disease is the first cause of death. For acute ischemic stroke patients, endovascular therapy is a very important supplementary treatment to improve neurological outcome, in case of thrombolytic therapy failed. Factors associated with clincal outcome of acute ischemic patients including baseline, comorbidity, onset to treatment time and so on. Observational studies indicated that, compared to general anesthesia, conciouse sedative ischemic stroke patients may have lower death, better neurological improvement. This indicated that management of anesthesia may effect neurological outcome. However, the research about relationship between acute ischemic stroke and anesthesia management is merely focuse on anterio circulation population,while posterior circulation ischemia account for a large amont of stroke and prospective research is need to demonstrate the association between anesthesia management and neurological outcome.

2. NUMBER of PARTICIPANTS

In total, 88 patients will be included in the study.

3. DURATION OF THIS STUDY

This study will last 3 years and we will collect your postoperative information until 90 days postoperatively.

4. PROCESS OF THIS STUDY

If you are willing to participate in the study,please sign this informed consent, and you will be examed including:

- Physical examination and medical history inquiry
- Vital signs:respiratory, body temperature, heart rate,blood pressure.
- Neurological scales: cognitive function, delirium, living quality as well as physical status

- Blood test
- Electrocardiography

If you met the inclusion and exclusion criteria, neuro-radiologist as well as anesthesiologist will evaluate your safety and with the agreement of both of them, you could be allocated into two groups randomly. With the computer-genrated table. you will be randomly allocated to receive one of anesthesia management in an equal chance.We will implete your anesthesia according to your group. During the whole study, we will collect your response to different anesthesia methods and your health status through closely intraoperative monitoring. This study will compare your post-treatment neurological outcome, complication, to find out which anesthesia treatment is better for acute posterior circulation ischemic patient, and final to optimize treatment of patients as you.

5. THE DIFFERENCE OF TWO ANESTEHSIA MANAGEMENT

There are most common clinical used anesthesia treatment for your condition, general anesthesia and conciuous sedation. However, considering there is no clinical trial to answer this question,it is still unclear which treatment s better. According to experience, general anestheisia may supply a safer airway management. Compared to conciuous sedation, you may have a lower chance of respiratory dysfunction for secured airway. Nevertheless, general anesthesia has a higher chance of circulation fluctuation and higher chances of intraoperative hypotension. Moreover, conciuous sedative patients are awake during the procedure and be able to do neurological evaluation at any time, to assess the neurological status. conciuous sedative patients may under light agitate status and unabe to complete surgery. Therefore, we still unable to answer the question which treatment is better. In conclusion, the purpose of this study is to find out which anesthesia treatment is better for acute posterior circulation ischemic stroke patients and finally to improve the treatment you future patients.

6. OTHER TREATMENT CHOICE

In clinical practive, the anesthesia management for acut stroke patients includes general anesthesia and conscious sedation. If you do not participate in this study, you can choose your anesthesia treatment according to your anesthesiologist's suggestion.

7. WHO SHOULD NOT PARTICIPATE in the STUDY

If you have following condition, you should not participate in the study：

1) Anterior circulation occlusion
2) GCS≤8,
3) Intracranial hemorrhage
4) Seizure or severe agitation
5) Intubated before treatment
6) Unconsciousness
7) Known allergy to anesthetics or analgesics
8) loss of airway protective reflexes and/or vomiting on admission

8. POSSIBLE BENEFITS of PARTICIPATING in the STUDY

Your prognosis may or may not improve as a result of participating in this study, and the information from this study will help determine which anesthesia management are safer and more effective in treating other patients with similar conditions of yours.

9. POSSIBLE ADVERSE REACTIONS, RISKS and DISCOMFORT, INCONVENIENCES of PARTICIPATING in the STUDY

The monitoring methods, anesthesia methods, anesthetic drugs and anesthesia maintenance used in this study are all routine clinical practice. It is possible that related discomfort or adverse event will happened during your anesthesia and operation, including respiratory depression, circulation depression, arrest, cardiac arythm, myocadial infarction, pulmonary embolism, drug adverse react as well as cerebrovascular complication (hemorrhage and infarction) If you experience adverse reactions or discomfort due to surgical procedures, anesthesia, or changes in your condition during the course of the study, the researchers will make corrections promptly.

During the study, you need to undergo doctors inquiry, laboratory tests and questionnaire, which may cause inconvenience to you.

10. CONFIDENTIALITY of PERSONAL INFORMATION

Your medical records (study records /CRF, lab sheets, etc.) will be kept intact at the hospital. Your doctor will record the results of tests and other tests on your medical record. Researchers, ethics committees, and drug regulators will be allowed access to your medical records. Any public reports on the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical data within the law.

11. HOW TO GET MORE INFORMATION?

You can ask any questions about this study at any time and get answers.Your anesthesiologist will be ready to answer any of your questions before, during and after the study.

12. RELATED EXPENSES

Anesthetic drugs and surgical procedures are not free of charge. If you combine the treatment and examination required for other diseases, and if the treatment fails, the cost of changing to other treatment is not free of charge. If any medical expense happened due to adverse event, you will be exempted from the charge.

13. YOU MAY VOLUNTARILY CHOOSE TO PARTICIPATE in the STUDY and WITHDRAW from the STUDY

Whether to participate in the study is entirely up to you. You may refuse to participate in the study or withdraw from the study at any time during the study, which will not affect your relationship with your doctor or affect your medical service or other benefits.

Before making decision, you can discuss with your family or friend,or your can talk with your doctor for any question, until you fully understand this study.

14. HOW THE STUDY MAY EFFECT YOUR LIFE?

You may feel the visit and examination uncomfortable and special arrangement is needed. You can consult your doctor in any steps of the study.

15. CONSULTING

If you have any related questions, please contact Dr.Liang Fa (phone: 010-67096658 or cell phone:18810084538).

If you have any concernes about your personal benefit, or you want to complain or express your concers about the study, please contact the Ethics Committee of Beijing Tiantan Hospital of Capital Medical University (phone: 010-67098555).

SIGNATURE PAGE of AGREEMENT

Study tile: Choice of ANesthesia for EndoVAScular Treatment of Acute Ischemic Stroke at Posterior Circulation

Principal investigator: Ruquan Han,Beijing Tiantan Hospital,CMU

DECLARATION of CONSENT

I have read the introduction about the study above and have the opportunity to discuss with doctors and ask the questions about the study. All my questions have been answered satisfactorily.

I am aware of the possible risk and benefits of participating in this study. I know that participating in the study is voluntary. I have taken it into full consideration, and known that:

- I can ask my doctor for more information at any time.
- I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

I am also aware that if I withdraw from the study, especially if I withdraw due to medication, it will be of great benefit to the whole study if I tell my doctor about my condition and complete the corresponding physical examination and physical and chemical inspection.

If I need to take any other medication due to a change in my condition, I will consult my doctor beforehand or tell him afterwards truthfully.

I agree that the ethics committee of the drug regulatory authority or the representative of the sponsor may have access to my research information.

I will be provided with a signed and dated copy of the informed consent.

In the end, I agreed to participate in the study and promised to follow my doctors advice as much as possible.

Signiture of patient/legal relative: _____

Relation: : _____

Date:_____**(yyyy/mm/dd)**

I confirm that I have explained the details of the trial to the patients, including its rights and possible benefits and risks, and have given them a signed copy of the informed consent.

Aignature of doctor: _____

Date: _____**(yyyy/mm/dd)**

Supplementary file 3 Measurement glossary

Physiological parameters		
Acronyms	**Full Names**	**Definition and Measurement description**
SBP	systolic blood pressure	Recorded 10 min before treatment and every 10 min during procedure in case report form (CRF) table, every 5 min in electronic medical record system. Target value:>140 mmHg, <180 mmHg.
DBP	diastolic blood pressure	Recorded 10 min before treatment and every 10 min during procedure in CRF table, every 5 min in electronic medical record system. Target value:>105 mmHg
FiO_2	inspired oxygen fraction	Recorded 10 min before treatment and every 10 min during procedure in CRF table, every 5 min in electronic medical record system.
$PaCO_2$	arterial partial pressure of carbon dioxide	Tested through arterial line access. Tested every 1 hour during endovascular therapy (EVT).
$ETCO_2$	end-tidal carbon dioxide	Recorded 10 min before treatment and every 10 min during procedure in CRF table, every 5 min in electronic medical record system.
BIS	bispectral index	Recorded 10 min before treatment and every 10 min during procedure in CRF table, every 5 min in electronic medical record system.
ECG	electrocardiography	Recorded 5 min in electronic medical record system.
HR	heart rate	Recorded 10 min before treatment and every 10 min during procedure in CRF table, every 5 min in electronic medical record system.

SpO_2	pulse oxygen saturation	Recorded 10 min before treatment and every 10 min during procedure in CRF table, every 5 min in electronic medical record system.
BP	blood pressure	Non-invasive blood pressure on either arm, measured every 5 min during procedure. Recorded 10 min before treatment and every 10 min during procedure in CRF table, every 5 min in electronic medical record system.
Glu	serum glucose	Tested before EVT treatment. During EVT, tested every 1 hour. Target value: 70-140 mg/L
MAP	mean artery pressure	Recorded 10 min before treatment and every 10 min during procedure in CRF table, every 5 min in electronic medical record system.
ABG	arterial blood gas	Monitored before treatment and every one hour during treatment, including Na+, K_+, Cl_-, $PaCO_2$, PaO_2, PH, glucose.
Evaluation		
Acronyms	**Full Names**	**Definition and Measurement description**
mRS	modified Rankin scale	Measured before treatment, 24h and 90 days after treatment
NIHSS	National Institute of Health stroke scale	Measured before treatment, 24h and 90 days after treatment
mTICI	modified Thrombolysis in Cerebral Infarction	Measured before EVT and immediately after recanalization.
GCS	Glasgow coma score	Measured before treatment, 24h and 90 days after treatment
pc-ASPECTS	post-circulation Alberta Stroke Program Early CT Score	Measured before treatment
Work flow		

Name	Definition and description
Onset to door	The duration between patient last know to be well and arriving to radiological suite.
Door to groin puncture	The duration between patient arriving at radiological suite and groin puncture initiating.
Puncture complete	The duration between groin puncture initiating and puncture completing.
Groin puncture to recanalization	The time duration between puncture complete and recanalization.
Recanalization time	The time duration between onset to recanalization success.
Recover time	The time duration between pressing against the puncture site and transferring to NICU.