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Intraoperative intensive blood pressure management strategy and the outcome of patients who had an acute ischaemic stroke undergoing endovascular treatment under general anaesthesia: study protocol for a prospective randomised controlled trial

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Background Endovascular thrombectomy is the recommended treatment for acute ischaemic stroke, but the optimal blood pressure management strategy during the procedure under general anaesthesia remains controversial. In this study protocol, we propose an intraoperative intensive blood pressure range (110–140 mm Hg systolic blood pressure) based on a retrospective analysis and extensive literature review. By comparing the outcomes of patients who had an acute ischaemic stroke undergoing mechanical thrombectomy under general anaesthesia with standard blood pressure management (140–180 mm Hg systolic blood pressure) versus intensive blood pressure management, we aim to determine the impact of intraoperative intensive blood pressure management strategy on patient prognosis.

Methods and analysis The study is a double-blinded, randomised, controlled study, with patients randomised into either the standard blood pressure management group or the intensive blood pressure management group. The primary endpoint of the study will be the sequential analysis of modified Rankin Scale scores at 90 days after mechanical thrombectomy.

Ethics and dissemination The study has been approved by the ethics committee of Shanghai Changhai Hospital with an approval number CHEC2023-015. The results of the study will be published in peer-reviewed international journals.

Trial registration number ChiCTR2300070764.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study was to explore the effects of different intraoperative blood pressure levels during endovascular thrombectomy on patient functional outcomes 90 days after surgery for acute brain stroke.
⇒ The study will provide evidence for optimising intraoperative blood pressure management of patients undergoing mechanical thrombectomy.
⇒ A large number of patients who had an acute stroke are admitted to our centre each year.
⇒ We have a dedicated team of anaesthesiologists.
⇒ The study may not be generalised to other surgical populations since it is a single-centre study.

INTRODUCTION

Acute stroke is a leading cause of death and disability in adults worldwide.[1] Despite advancements in treatment methods, the mortality rate of patients who had a stroke in high-income countries has decreased over the years, while the rate in low-/middle-income countries continues to rise.[2] Endovascular thrombectomy (EVT) has become the standard treatment for acute ischaemic stroke (AIS) caused by obstruction of the anterior cerebral circulation.[3] With enhanced awareness and rapid imaging development, the treatment window for acute stroke has been extended to 24 hours, leading to a higher implementation rate of EVT.[4 5] However, a significant number of patients still have poor clinical outcomes, with only about 50% of patients regaining neurological function after 3 months.[4–11]

In addition to vascular recanalisation, several factors influence the clinical outcome of patients with AIS. Among these factors, perioperative blood pressure plays a crucial role and is considered a significant measure to enhance the clinical prognosis of patients.[12] Cerebral perfusion pressure is subject to fluctuations caused by cerebral blood flow interruption, reperfusion injury and abnormal brain autoregulation.[13] In patients requiring general anaesthesia following AIS, the circulatory system may be inhibited to varying degrees during the perioperative period,

potentially exacerbating the impairment of cerebral autoregulation.[14] Thus, optimal management of blood pressure during EVT continues to be an area of uncertainty and is currently based on expert opinion and consensus rather than robust evidence from randomised clinical trials.[15 16]

It has been suggested that maintaining a high level of perioperative blood pressure, while beneficial for cerebrovascular perfusion, increases the risk of bleeding during surgery. Studies have also shown an association between adverse neurological outcomes and the incidence and duration of hypotension during endovascular therapy EVT.[17 18] However, there is currently a lack of prospective randomised controlled studies providing evidence for optimal blood pressure management in patients who had an AIS during EVT. A recently published meta-analysis included nine non-randomised studies, five of which suggested a positive association between intraoperative hypotension and adverse postoperative outcomes, while four did not clearly establish the association. Additionally, only three studies involved mentioned specific intraoperative systolic blood pressure (SBP) targets of 140–180 mm Hg.[19]

Currently, there is insufficient evidence to support the notion that increasing cerebral blood flow through elevated SBP during EVT improves neurological outcomes. Petersen *et al* explored the relationship between maintaining mean arterial pressure above the upper limit of autoregulation and neurological recovery at discharge and 90 days after surgery, and have identified a potential association that may lead to an increased risk of haemorrhagic transformation and symptomatic intracranial haemorrhage.[20] Hussain *et al* reported that patients who had an AIS who maintained a lower SBP during EVT have a better prognosis. Intraoperative controlled SBP has been suggested as an independent predictor of better postoperative prognosis. However, the study did not propose a specific target value for blood pressure management.[21]

In clinical practice, blood pressure is often reduced in patients who had an AIS after general anaesthesia induction, and vasoactive agents are required to maintain normal or higher blood pressure. This approach may be based on the observation that prolonged hypotension is associated with an increased incidence of cognitive dysfunction within 48 hours after surgery.[22] A randomised controlled trial on circulatory management in patients who had an AIS during EVT demonstrated that an SBP target of 130–150 mm Hg was safe.[23] Furthermore, a collaborative pooled analysis of 1332 patients undergoing thrombectomy for AIS indicated that a baseline SBP below 110 mm Hg was associated with increased perioperative mortality and disability.[24] Based on a comprehensive literature review and our centre's practical management strategies, we propose an intensive blood pressure management strategy (SBP range 110–140 mm Hg) during EVT under general anaesthesia. During our preliminary study and clinical experience, we believe that this strategy is safe and non-inferior to traditional blood pressure management in terms of its impact on postoperative outcomes.

Thus, we designed a prospective, single-centre, randomised, controlled trial to evaluate the effects of different intraoperative blood pressure levels (SBP between 140 and 180 mm Hg vs SBP between 110 and 140 mm Hg) during EVT under general anaesthesia in patients with radiation-proven large-vessel occlusive AIS. The primary objective was to evaluate the impact of intraoperative blood pressure management during EVT on patient functional outcomes at 90 days postoperatively.

METHODS AND ANALYSIS

The study is a double-blinded, randomised, controlled study. The objective of this study was to determine whether the intensive blood pressure management strategy is safe and non-inferior to the traditional blood pressure management strategy in terms of modified Rankin Scale (mRS) scores at 90 days after EVT. The trial received approval from the ethics committee of Shanghai Changhai Hospital on 10 April 2023, with the approval number CHEC2023-015. Subsequently, it was registered at the China Clinical Trials Registry under the registration number ChiCTR2300070764. The pretrial was completed on 5 July 2023 with 10 patients. The formal trial has been started on 1 September 2023, and we plan to enrol participants for 2 years. The overall trial flow chart is presented in figure 1, and the trial schedule is outlined in table 1.

Study population

Patients admitted to the emergency department of our hospital from September 2023 to September 2026 with AIS and large vessel occlusion confirmed by cranial imaging examination, who require EVT under general anaesthesia, will be screened and enrolled. Prior to surgery, patients or their legal representatives will be fully informed about the objectives, risks and benefits of this study. Written informed consent will be obtained from the patients' legal representatives. The investigators will complete the case report form in accordance with the listed items, which include age (in years), sex (male or female), height, weight and ASA classification. Patients who do not meet the inclusion criteria will be excluded. Additionally, enrolled patients have the right to discontinue and withdraw from the trial at any time, but must provide accurate medical history and respond to the investigator's questions. The patients' personal data will be protected and stored by the investigator in a numbered and secure cabinet.

Inclusion criteria

To be eligible for inclusion in the study, participants must meet all of the following criteria:

- 18 years old ≤age ≤75 years old.
- Clinical diagnosis of AIS with imaging evidence of large vessel occlusion in the anterior or posterior

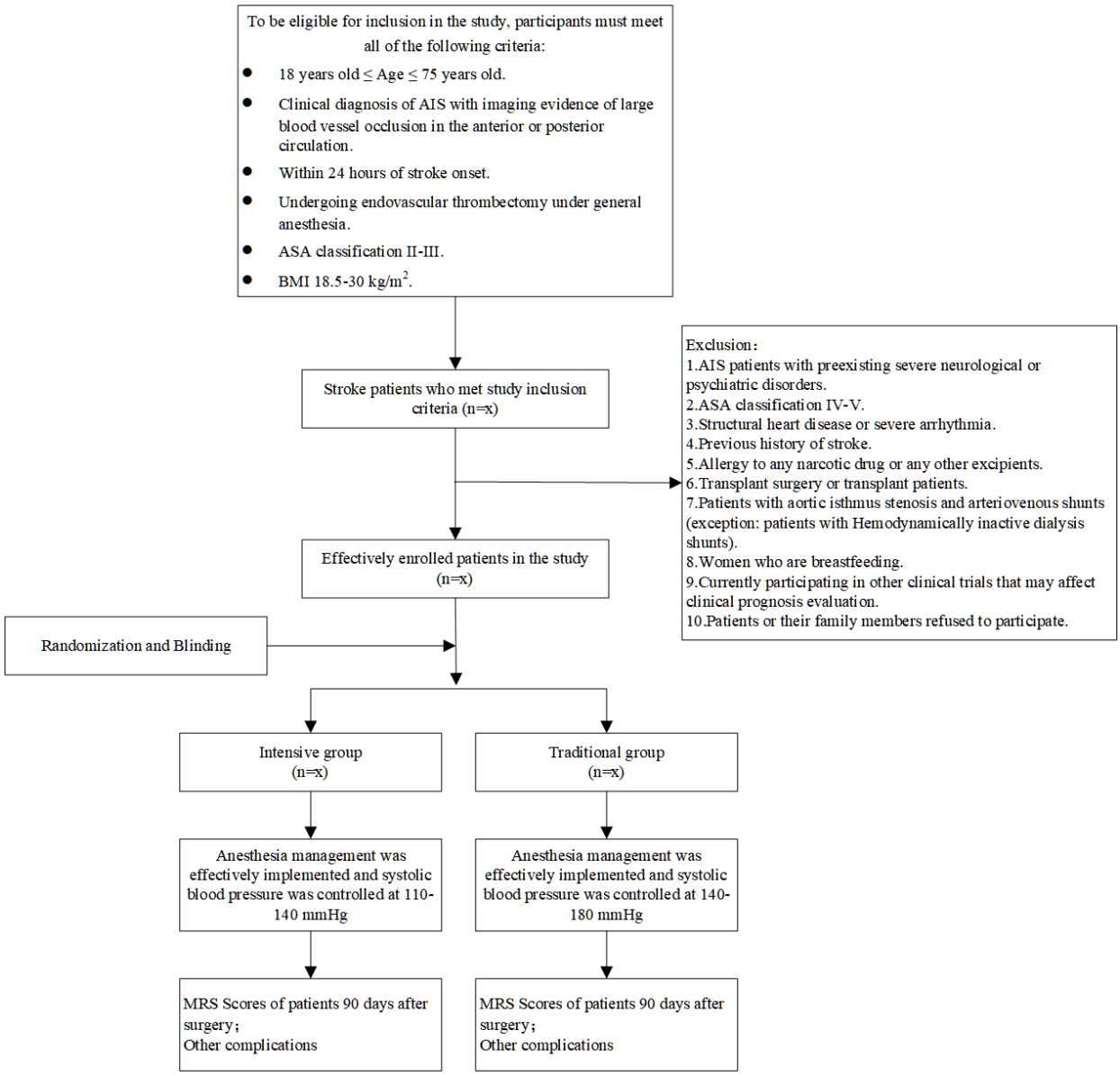

Figure 1 Flow chart of the patient allocation. AIS, acute ischaemic stroke; BMI, body mass index; mRS, modified Rankin Scale.

circulation. Confirmation of an intracranial large vessel occlusion of the anterior circulation, specifically within the intracranial segment of the internal carotid artery, the M1 segment of the middle cerebral artery (M1), and the proximal M2 segment of the middle cerebral artery (M2), must be achieved through the implementation of computed tomography angiography imaging. Haemorrhage has to be ruled out by CT or MRI imaging.

- Within 24 hours of stroke onset.
- Undergoing EVT under general anaesthesia.
- ASA classification II-III.
- Body mass index 18.5–30 kg/m^2.

Exclusion criteria

Potential subjects were excluded from the study if they met any of the following criteria:

- Patients who had an AIS with pre-existing severe neurological or psychiatric disorders.
- ASA classification IV-V.
- Structural heart disease or severe arrhythmia.
- History of stroke.
- Allergy to any narcotic drug or any other excipients.
- Transplant surgery or transplant patients.
- Patients with aortic isthmus stenosis and arteriovenous shunts (exception: patients with haemodynamically inactive dialysis shunts).
- Women who are breast feeding.
- Currently participating in other clinical trials that may affect clinical prognosis evaluation.
- Patients or their family members refused to participate.

Table 1 Timelines for patient screening, study interventions and outcome evaluation

Timepoint	Preoperative visit	During surgery	36 hours after surgery	3 days after surgery	7 days after surgery	90 days after surgery
Enrolment						
Inclusion criteria	×					
Exclusion criteria	×					
Written informed consent	×					
Recording baseline feature	×					
Randomisation and blinding	×					
Allocation	×					
NIHSS score	×					
Imageological examination	×		×		×	×
Interventions						
General anaesthesia		×				
Intensive group: 110–140 mm Hg		×				
Traditional group: 140–180 mm Hg		×				
Vasoactive agent		×	×			
Postoperative evaluation						
QoR-15				×		
HRQOL						×
NIHSS score						×
mRS score						×
Disability assessment						×
Ultimate outcome						×
Postoperative length of hospital stays						×

HRQOL, Health-related Quality of Life; mRS, Modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; QoR-15, Quality of Recovery-15 score.

Elimination criteria

- Change of operation method, without intravascular thrombectomy.
- Patients and their families refused to participate after the study began.

Randomisation and blinding

To avoid selection bias, this study employed randomisation and allocation concealment. The randomisation and concealed allocation were conducted by a medical statistician prior to the commencement of the trial. Patients were randomly assigned in a 1:1 ratio to either the intensive blood pressure management group (Intensive group) or the traditional blood pressure management group (Traditional group) using a computer-generated random number table. The randomisation sequence was generated based on a minimisation algorithm to ensure balance of key influencing factors. Patients were also stratified according to the following criteria: (1) time from onset to recanalisation (stroke ≤6 hours, 6 hours <stroke ≤12 hours, 12 hours <stroke ≤18 hours, and 18 hours <stroke ≤24 hours); (2) baseline National Institute of Health Stroke Scale (NIHSS) score (<17, ≥17); (3) according to the age of patients (18 years ≤age <35 years, 35 years ≤age < 60 years, 60 years ≤age <75 years).

The study participants were divided into several groups: the research coordinator, clinical anaesthesia group, evaluation and follow-up group and data statistical analysis group. A double-blind method was used to ensure impartiality. The study coordinators were responsible for screening and randomly assigning patients, as well as overseeing the study process and coordinating personnel and materials. Meanwhile, the clinical anaesthesia team strictly adhered to the research protocol and recorded relevant data during each operation, without making any unauthorised changes to the management approach. Subsequently, the evaluation and follow-up group assessed the patients' condition, symptoms and signs after each operation, conducting necessary follow-up tasks related to the study. Following completion of the study, the data statistical analysis group promptly organised and analysed the collected data. Throughout the study, only the research coordinators and members of the clinical anaesthesia team had knowledge of the patient grouping and specific details regarding intraoperative patient haemodynamic

management. This information was kept confidential from the evaluation and follow-up team, data statistical analysis team, patients and their families. Moreover, the laptop used for data collection was password protected and managed by members of the statistical analysis group.

Anaesthesia management

All subjects who met the study's inclusion and exclusion criteria were admitted to the operating room after randomisation. Peripheral venous access was promptly established, and a balanced fluid infusion was administered intravenously. The rate of infusion was carefully adjusted based on the duration of fasting following the patient's admission to the room. ECG monitoring, including non-invasive blood pressure, oxygen saturation and ECG, was initiated. The radial artery was punctured to monitor blood pressure changes, and vital signs before anaesthesia induction were recorded. Intravenous injections of midazolam 0.05 mg/kg, etomidate 0.3 mg/kg, rocuronium 0.6 mg/kg and sufentanil 0.5 µg/kg were administered. The rapid sequence induction and intubation strategy was implemented in this clinical setting. Throughout the entire operation, a temperature probe was placed through the nose to monitor the temperature of the middle part of the oesophagus. Patients undergo routine temperature protection strategies throughout the entire surgical procedure in accordance with our institutional protocol.

Anaesthesia was maintained with propofol 5 mg/(kg h) and remifentanil 0.2 µg/(kg min). During the perioperative period, the clinical anaesthesia team adjusted the continuous infusion dose of anaesthetic agent as needed based on the patient's condition and the requirements of the operation. Haemodynamic parameters, including heart rate and blood pressure, will be diligently monitored to ensure stability. If needed, vasopressors such as phenylephrine or norepinephrine, as well as antihypertensives like urapidil hydrochloride or nicardipine hydrochloride, will be carefully considered to maintain stable haemodynamics while prioritising patient safety. Additionally, detailed documentation will be maintained regarding the dosage and timing of the administered vasopressors and antihypertensives. Arterial blood gas, arterial partial pressure of oxygen (PaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$) and blood glucose levels were assessed both after induction of anaesthesia and at the conclusion of the surgical procedure.

After the surgical procedure, all administration of anaesthetics, both intravenous and inhaled, was promptly discontinued. To counteract any remaining muscle relaxants, neostigmine combined with atropine was administered intravenously. Additionally, flumazenil was intravenously given to reverse the sedative effects of midazolam. During the anaesthesia recovery phase, the SBP of patients who underwent vascular recanalisation was carefully controlled, maintaining it within the range of 120–160 mm Hg. The vasoactive agents employed to regulate blood pressure were the same as those used during the maintenance period of anaesthesia. Extubation of the endotracheal tube was performed once the patient's respiratory function had sufficiently recovered, indicated by a tidal volume of 300 mL or more, and oxygen saturation remained above preoperative levels. On transfer to the postoperative ward, the patient's circulatory management continued to maintain a SBP within the range of 120–160 mm Hg. Vasoactive agents were used as needed for adjustments, and the patient's fluid intake and output were regulated according to their specific medical condition.

All thrombectomy procedures were provided by specialist interventional radiologists. Device choice and thrombectomy technique were at the discretion of the interventional radiologist. The results of recanalisation were evaluated by interventional radiologists according to the expanded Treatment In Cerebral Ischemia Scale, and the recanalisation was effective if it exceeded grade 2b.

Outcomes

Primary outcomes

The primary outcome is the recovery of neurological function 90 days after surgery. The mRS was used to assess the recovery of neurological function. The mRS is a widely recognised tool for evaluating the outcome of stroke treatment, ranging from 0 to 6: 0=no symptoms; 1=ability to perform all daily activities without significant disability despite symptoms; 2=mild disability, unable to perform all preillness activities but does not require assistance and can manage personal affairs; 3=moderate disability, requiring some assistance but able to walk without aid; 4=severe disability, unable to walk independently and meet personal needs without assistance; 5=severe disability, bedridden, incontinent, and requiring constant care; 6=death.

Secondary outcomes

- Intracerebral haemorrhage (ICH): (a) symptomatic ICH based on National Institute of Neurological Disorders and Stroke (NINDS) criteria: ICH confirmed by brain imaging (or autopsy) within 36 hours from baseline with an increase in NIHSS score of ≥1 point, or death; (b) symptomatic ICH based on The Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria: large parenchymal haemorrhage on imaging (PH2) with an increase of ≥4 on the NIHSS score within 36 hours from baseline, or death; (c) symptomatic ICH based on Heidelberg Bleeding Classification; (d) any type of ICH on cranial imaging within 7 days of treatment; (e) any symptomatic ICH within 90 days of thrombectomy therapy. ICH will be assessed by CT imaging with central adjudication.
- The occurrence of postoperative complications, including pulmonary complications, cardiovascular complications and acute kidney injury.
- Postoperative nausea, vomiting and headache experienced by the patient.

- Imaging endpoints: (a) increased infarct volume, as assessed by imaging (head MRI) within 24–48 hours of onset; (b) oedema volume, as assessed by imaging (head CT) during the first day of onset.
- 7-day death or disability analysed sequentially by NIHSS score.
- Death and severe disability within 3 months (mRS Score 3–6); death within 3 months; disability within 3 months (mRS Score 3–5).
- Health-related quality of life at 3 months, assessed by the European Five-Dimension Health Scale of Quality of Life (EQ-5D).
- Quality of recovery: in evaluating the recovery of patients who have regained consciousness and exhibit appropriate responsiveness, the assessment of their recovery quality is conducted on the third day post surgery, using the Quality of Recovery-15 (QoR-15) instrument. The QoR-15 is a patient-reported outcome questionnaire specifically designed to gauge the quality of recovery following surgical procedures and the administration of anaesthesia. Furthermore, it is noteworthy that the validation of the QoR-15 instrument has also been conducted in the Chinese population, ensuring its applicability and accuracy within this context.
- Length of hospital stay, accommodation and hospital expenses.

Sample size calculation

Based on the meta-analysis conducted by Hermes *et al*, the proportions of patients with mRS Score 0–6 were reported as 10.0%, 16.9%, 19.1%, 16.9%, 15.6%, 6.2% and 15.3%, respectively.[3 25 26] Additionally, the proportion of patients with a poor prognosis (mRS Score 3–6) was determined to be 47.52%. For our study design, we used the PASS V.18 software to calculate the sample size. We aimed to achieve a power of 90% and assumed a 40% proportion of patients with a poor outcome (mRS 3–6) in the normotensive group. Considering a potential dropout rate of 10% among the study subjects, our estimated sample size is 318 subjects.

Statistical analysis

The intention-to-treat principle will be used in the analysis of the results in this study. Baseline data will be calculated based on the group to which the patients were randomised. For patients who dropped out, data from the time of randomisation until the last available data will be included in the analysis. The primary outcome and classified secondary outcomes will be analysed using the χ^2 test. For small sample size analysis, Fisher's test can be used. Continuous endpoints, such as the 90-day EQ-5D, will be described as means or medians. If the data are skewed, the Wilcoxon test will be used. Otherwise, mixed models will be used to analyse health utility scores over time. The main analysis will not adjust for confounding factors. Safety data will be analysed using descriptive statistics. The reporting of any serious adverse event, the occurrence of selected serious adverse events and the interruption of the assigned treatment due to a serious adverse event will be classified using Medical Dictionary for Regulatory Activities terms. The heterogeneity of the primary endpoint event will be assessed based on the following stratification factors: age (18 years ≤age < 35 years, 35 years ≤age < 60 years, 60 years ≤age < 75 years), time from symptom onset to mechanical thrombectomy (stroke ≤6 hours, 6 hours <stroke ≤12 hours, 12 hours <stroke ≤18 hours and 18 hours <stroke ≤24 hours), systolic and diastolic blood pressures (above or below the mean), race, putative AIS type and baseline NIHSS score (above or below the median).

The statistical analysis will be described in a prespecified statistical analysis plan and will include two interim analyses. The first interim analysis will be performed when 30% of the 90-day follow-up data has been collected, and the second interim analysis will be performed when 60% of the 90-day follow-up data has been collected. The external Data and Safety Monitoring Board (DSMB) will be governed by the Haybittle-Peto rule, with an alpha of less than 0.001 considered to indicate a significant effect at the interim analysis. The conventional significance level (alpha=0.05) will be used for the last interim analysis, considering that only two interim analyses will be performed and subsequent analyses will require further confirmation. The DSMB will regularly monitor serious adverse events (eg, death, symptomatic intracranial haemorrhage and neurological deterioration), and any occurrence of excess serious adverse events will trigger a discussion about study termination.

DISCUSSION

The primary aim of this study is to evaluate the effects of different intraoperative blood pressure levels during EVT under general anaesthesia in patients with AIS on patient functional outcomes at 90 days postoperatively.

Acute stroke is a leading cause of death and disability globally. The 2019 Global Burden of Disease report revealed that the lifetime risk of stroke in the Chinese population was remarkably high, reaching 39.3%, the highest worldwide. AIS, the most common type of stroke in China, accounts for approximately 69.6%–70.8% of all strokes, resulting in a 1-year mortality rate of 14.4%–15.4% and a disability rate of 33.4%–33.8%. These alarming statistics impose a significant social and economic burden on the country.[27 28] Effective treatment of AIS relies on rapid vascular recanalisation, rescue of ischaemic penumbra, reduction of core infarct volume and timely restoration of occluded vascular perfusion, which collectively enhance patient prognosis.[29]

While intravenous thrombolysis with recombinant tissue plasminogen activator is an effective method for achieving early vascular recanalisation in AIS, its usefulness is limited by a strict time window (within 4.5 hours). In recent years, while mechanical thrombectomy has greatly improved successful recanalisation rates in

patients who had an AIS caused by large vessel occlusion, a significant proportion of patients still experience poor clinical outcomes. Apart from vascular recanalisation, other factors such as baseline NIHSS score, recanalisation time, age, hypertension, blood glucose level, history of atrial fibrillation and infarct location also contribute to the clinical prognosis of patients who had an AIS.[30 31]

Currently, the optimal level of blood pressure control during mechanical thrombectomy under general anaesthesia is still controversial. Some expert consensus suggests maintaining blood pressure below 180/105 mm Hg during and up to 24 hours after the procedure. However, the evidence supporting this recommendation is of low quality, and specific blood pressure management targets are lacking.[16] Some studies have indicated that maintaining blood pressure at a high level (SBP 140–180 mm Hg) benefits cerebral vascular perfusion but increases the risk of bleeding during thrombectomy.[32] Higher blood pressure levels require larger doses of vasoactive agents. In the Sedation vs. Intubation for Endovascular Stroke Treatment (SIESTA), Anesthesia During Stroke (AnStroke) and The General or Local Anesthesia in Intra Arterial Therapy (GOLIATH) studies, single-centre randomised controlled trials of general anaesthesia for EVT in patients who had an anterior circulation stroke, all patients received vasoactive agents (eg, norepinephrine) to maintain a high level of SBP.[33–35] In contrast, previous studies have suggested that a lower intraoperative SBP is associated with a favourable outcome in patients who had an AIS undergoing mechanical thrombectomy.[21] Additionally, lower intraoperative maximum SBP has been identified as an independent predictor of good outcome, indicating that SBP may be the most significant haemodynamic variable to monitor during mechanical thrombectomy. Despite these findings, specific values for blood pressure management have not been proposed.

A recent post hoc analysis of a single-centre prospective study found that standard blood pressure before intraoperative recanalisation during endovascular therapy did not show an association with poor functional outcome. However, higher intraoperative prerecanalisation SBP (>163 mm Hg) and MAP (>117 mm Hg) were associated with worse functional outcomes.[36] Another recent study indicated that the use of norepinephrine to maintain high blood pressure may have an increased incidence of cognitive dysfunction within 48 hours after surgery, which is not beneficial for postoperative brain function recovery.[22] This suggests that maintaining blood pressure at a standard level may be safer and more conducive to brain function recovery after surgery.

A collaborative pooled analysis conducted by Maïer *et al* investigated the relationship between baseline blood pressure and mortality and disability in 1332 patients who underwent thrombectomy for AIS. The results revealed that patients with a baseline blood pressure below 110 mm Hg had a higher risk of perioperative mortality and disability. The authors emphasised the potential influence of initial blood pressure management on outcomes of EVT in patients with AIS. Additionally, they found that baseline SBP was associated with all-cause mortality and prognosis.[24] Intraoperative cerebral blood flow is primarily dependent on the autoregulation of cerebral perfusion pressure and cerebral vasomotion. However, a retrospective cohort study involving 358 391 patients did not find any evidence linking intraoperative hypotension within the specified range (intraoperative MAP <55 mm Hg or a >30% decrease in MAP) to early perioperative stroke occurring within 7 days after surgery.[37] These findings emphasise the significance of perioperative cerebral blood flow autoregulation in preventing ischaemic stroke. Considering patient safety as a priority, we have therefore decided to establish the lower limit for SBP in our trial at 110 mm Hg.

To sum up, there is considerable uncertainty regarding the optimal management of blood pressure during EVT under general anaesthesia. Haemodynamic management practices for these patients undergoing general anaesthesia are primarily based on expert opinions and consensus rather than high-quality clinical randomised controlled prospective studies. Consequently, elucidating the impact of maintaining blood pressure at a standardised level during EVT under general anaesthesia on the prognosis of patients who had an AIS can significantly contribute to optimising clinical blood pressure management in these settings.

Trial status

The pretrial was completed on 5 July 2023 with 10 patients. The formal trial will begin on 1 September 2023, and we plan to enrol for 2 years. End of follow-up of patients will be completed approximately 90 days after the last enrolment.

Dissemination

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

Audits

The data monitoring committee will conduct audits through regular interviews, letters or telephone. The data monitoring committee reserves the right to audit the recruitment of patients at any time. The auditing process will be independent from the investigators.

Amendments to the protocol

Any deviations from the protocol will be fully documented in a report form, reported to all regulatory bodies and thoroughly recorded in a protocol deviation log. The PI will determine the protocol amendments. Protocol amendments will be sent as updated protocols to investigators. A copy of each revised protocol will be added to the investigator site file. The protocol will also be updated in the clinical trials registry website.

Strategies to improve the adherence to protocols

The anaesthesiologist who implements anaesthesia in this study will be trained to obey the standardised procedure.

The investigator staff will be well trained to perform preoperative recruitment, assessment and postoperative follow-up. We will train the whole study team to standardly use the assessment scales involved in this study. Moreover, the investigator who will do the assessments will be blind to the intervention.

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Contributors BL and LB designed the study. LB was the principal investigator and guarantor. BL, TN and YD were the main coordinators of the study. BL, TN, YD, LB , KP and LL conducted the study. YD provided statistical and epidemiological support. BL and TN wrote the article with the support of LB. All the authors revised and approved the final version of the manuscript.

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Competing interests None declared.

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