


BMJ Open Safety of surgical Treatment In severe primary Pontine haemorrhage Evacuation (STIPE): study protocol for a multi-centre, randomised, controlled, open-label trial

Qiang He ¹, Jiajing Wang,² Lu Ma,¹ Hao Li,¹ Chuanyuan Tao,¹ Chao You¹

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QH and JW contributed equally.

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¹Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, Sichuan, China

²Department of Post Anesthesia Care Unit, West China Hospital of Stomatology, Sichuan University, Chengdu, Sichuan, China

Correspondence to

Professor Chuanyuan Tao;
tcy106@163.com

ABSTRACT

Introduction Primary pontine haemorrhage (PPH) is the most devastating subtype of intracerebral haemorrhage and is associated with poor prognosis, especially for the severe patients. Although medical treatment (MT) is widely accepted, a large number of studies have shown surgical haematoma evacuation (HE) might dramatically reduce mortality and improve prognosis outcome in severe PPH (sPPH). However, evidence to clarify the safety of HE remains insufficient.

Methods and analysis The Safety of surgical Treatment In severe primary Pontine haemorrhage Evacuation study is a multi-centre, randomised, controlled, open-label trial, conducted from January 2022 to November 2024 in 20 tertiary hospitals in China. A total of 64 patients with sPPH will be randomly assigned to MT or HE group. Eligible patients will receive the corresponding treatment according to the result of randomisation. The primary outcomes are related to the safety of surgery including rate of symptomatic rebleeding at 3 days and rate of mortality and intracranial infection at 30 days. The secondary outcomes are the neurological function indexes following up at 30 days, 90 days, 180 days and 365 days.

Ethics and dissemination The clinical trial has been approved by the Biomedical Research Ethics Committee of West China Hospital of Sichuan University (unique identifiers: No. 2020-894). All results of the trial will be published in international peer-reviewed scientific journals and will be disseminated through scientific conferences. Academic dissertation will be published in a peer-reviewed journal.

Trial registration numbers NCT04647162, ChiCTR2000039679.

INTRODUCTION

Primary pontine haemorrhage (PPH) is defined as a type of brainstem haemorrhage occurring in the pons without structural lesions such as cavernous or arteriovenous malformations. The development of PPH is particularly relevant to the chronic hypertension. Although the incidence of PPH is low with 2–4 per 100 000 people annually,¹

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The clinical trial is the first multi-centre, randomised, controlled, open-label trial to evaluate safety of surgical treatment in patients with severe primary pontine haemorrhage in 20 Chinese tertiary hospitals.
- ⇒ The trial will provide evidence to clarify whether a lower mortality can be achieved by haematoma evacuation.
- ⇒ Our study focused on the safety study in patients with strict inclusion criteria which limits the generalisability.

it is the most catastrophic subtype of intracerebral haemorrhage (ICH) which affecting relatively younger populations aged 40–60.² An acute mortality was reported between 30% and 60%^{3–5} and long-term mortality over 60%.⁶ Severe PPH (sPPH) which is commonly defined as Glasgow Coma Scale score (GCS) <8 and haematoma volume (HV) ≥5 mL has a mortality of over 40% in 30 days.⁷

Guidelines from the American Heart Association/American Stroke Association (AHA/ASA) and European Stroke Organisation do not make definite recommendations for the treatment of PPH.^{8,9} Considering the possible surgical injury to vital structures around haematoma, many believe that surgical haematoma evacuation (HE) in brainstem may be harmful. Therefore, medical treatment (MT) for PPH is widely accepted despite the fact that the majority of patients eventually died under conservative management, especially in sPPH.

Since Finkelnburg first explored the brainstem haematoma,¹⁰ many studies have demonstrated that HE can decrease mortality and achieve a better clinical prognosis in PPH.^{5,11–17} Nevertheless, evidence for surgical HE largely consisted of non-randomised case

series or even expert opinions and were retrospective with innate limitation in study design. Moreover, these studies were often small with heterogeneous surgical timing, no description of the degree of haematoma clearance and limited follow-up. These limitations make it insufficient to show the superiority of HE over MT and make the optional treatment challenging. With the improvement of neurosurgical techniques as well as neuro-navigation and neurophysiological monitoring, iatrogenic surgical damage can be minimised as less as possible. The goal of this study is to clarify whether surgical HE treatment is safe in patients with sPPH.

METHODS

Objectives and study hypothesis

The objective of the clinical trial is to evaluate the safety of the surgical HE in comparison with MT in patients with sPPH. Our hypothesis is that surgical HE is safe and can reduce 30-day mortality.

Trial design

This Safety of surgical Treatment In severe primary Pontine haemorrhage Evacuation (STIPE) trial is an investigator-initiated, parallel (3:1 to surgical HE or MT), multicentre, randomised controlled open-label trial following the Consolidated Standards of Reporting Trials guidelines and will be conducted from January 2022 to November 2024 in 20 tertiary hospitals in China. The flow chart of the clinical trial is presented in [figure 1](#). Neurosurgeons involved in the study are senior investigators with good clinical experience in sPPH management. Moreover, all investigators are well trained centrally according to the requirements.

Study setting

The trial will take place in China. A total of 20 Chinese tertiary hospitals will participate in this study.

Eligibility criteria

1. Clinical diagnosis of PPH: patients have acute haemorrhage mainly in pons with a definite history of hypertension.
2. GCS 5–7 and HV \geq 5 mL on admission (the HV in intraventricular system being excluded).
3. Family members consenting to randomise and signing informed consent form.
4. Time from onset to admission less than 24 hours.
5. Age:18 years or older.

Exclusion criteria

1. Structural lesions such as brainstem cavernous malformation, arteriovenous malformation, aneurysm, tumour apoplexy.
2. GCS \geq 8 and HV $<$ 5 mL.
3. Time from onset to admission over 24 hours.
4. Patients with platelet count $<$ 100 000, international normalised ratio $>$ 1.4, or an elevated prothrombin time and activated partial thromboplastin time.

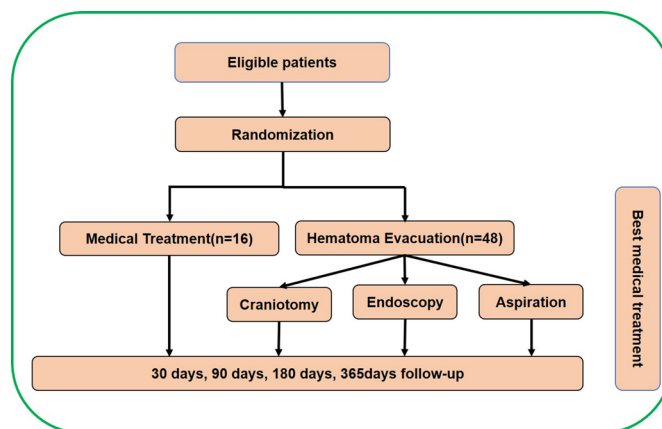


Figure 1 The flowchart of Safety of surgical Treatment In severe primary Pontine haemorrhage Evacuation trial.

5. Multiple ICH.
6. Accompanying hydrocephalus that requires surgical management
7. Irreversible brainstem failure (bilateral fixed, dilated pupils and extensor motor posturing, GCS \leq 4).
8. A history of ICH.
9. Any serious concurrent illness that would interfere with the safety assessments including hepatic, renal, gastroenterological, respiratory, cardiovascular, endocrinological, immunological and haematological disease.
10. Pregnant patients.
11. Patients' family members refuse HE.
12. Any other condition that the investigator believes would present a significant hazard to the subject if the investigational therapy were initiated.
13. Participating in another simultaneous trial of ICH treatment.

Sample size

The calculation of sample size depends on the outcome distribution from our previous work.¹¹ It was reported that 70.4% patients died with MT while only 30.4% died undergoing surgical HE after sPPH. A sample size of 60 would be required to demonstrate a significant level of 5% (two-sided) with 80% power. Considering the 6% missing rate during follow-up, the total sample size was 64 cases with 16 and 48 cases in MT and HE group, respectively.

Randomisation and blinding

After obtaining the consent from the patient's family, the patients who meet the eligibility criteria are randomly assigned 3:1 to HE or MT according to block randomisation method. Randomisation is undertaken using a central 24-hour randomisation service accessed by web in the central randomisation system. It is not possible to set blind because of the nature of the surgical intervention. However, the assessors are blinded to the grouping during follow-up. The patient's outcomes are recorded in electronic Case Reports Forms (eCRF) by researchers who remain blind to the patient allocation and the treatment.

Data collection and follow-up

Data collection will be performed using a web-based electronic data capture system (EDC system) by trained and experienced staffs and researchers. The data during follow-up will be collected by assessor who is blinded to the grouping and treatment. At the baseline and setting time point during follow-up, the EDC system mainly records basic data (age, gender, race, provenance, occupation), medical histories (primary symptom, operation history, and past history, family history, smoking and drinking history), imaging, laboratory and treatment information, and follow-up data (GCS score, Modified Rankin Scale (mRS) score and National Institutes of Health Stroke Scale (NIHSS) score, Extended Glasgow Outcome Scale (EGOS), 5-level EuroQol five dimensions questionnaire version (EQ-5D-5L)). Any adverse events (AEs) occurring during the study period are also recorded and must be reported to the principal investigator. Those data will be uploaded into EDC system in time.

Quality control

The quality control for this study relies on the strict inclusion of investigating centres where experienced neurosurgeons in stroke unit should be available, the creation of imaging centre which can provide accurate calculation of HV, the establishment of operating centre where standardised operative procedures and assessment of surgeon's ability and credential will be provided, and the development of follow-up centre to guarantee the acquisition and accuracy of follow-up results.

Data and safety monitoring

An independent Data and Safety Monitoring Board (DSMB) including neurosurgeons, neurologists, radiologists, statisticians and data managers will monitor the safety of this trial. The meeting will be held two times in a year to review the data. Extra meeting will be added when necessary. Interim analyses will be conducted. The DSMB has the right to terminate the trial if surgical treatment show disadvantage or a higher incidence of severe adverse effect (SAE) than MT. The SAE is defined as death. Both AEs and SAEs will be recorded in the eCRF in time and notify them to principal investigators within 24 hours.

Trial procedures

Based on the result of treatment allocation for eligible patients, the corresponding interventions will be conducted as soon as possible. The basic information for eligible patients will be collected. All researchers will be trained centrally and qualified according to the study requirements to reach the uniform standard.

Procedures in MT

Principles in MT will strictly follow the recommendation of 2015 ASA/AHA ICH guidelines.⁸ Specifically, temporal extra-ventricular drainage (EVD) should be performed in case of increased intracranial pressure due to delayed hydrocephalus although early onset of hydrocephalus is excluded in this trial.

Surgical procedures in HE

The modality of surgical performance in HE group is preferred by the treating neurosurgeon, including craniotomy, neuro-endoscopy and stereotactic aspiration.

Surgical principles include minimal brain attraction, slight aspiration, manipulation strictly limited within haematoma cavity, and electrocoagulation with small power when necessary. All surgical procedures will be conducted under the monitoring of intraoperative neurophysiological equipment (INPE). Haematoma clearance is done as much as possible in the guidance of the surgical principles.

Craniotomy

Patients in this subgroup receive HE by craniotomy.¹⁸ The patient's surgical position and approach are determined by experienced neurosurgeons in the surgical centre. In general, suboccipital, subtemporal, retrosigmoid or transcerebellar-middle cerebellar peduncle approach will be used depending on the haematoma location. The haematoma is evacuated under the help of microscope and INPE. A 'Rebleeding test' will be performed after haemostasis. Blood pressure will be slowly elevated to the level before the anaesthesia and maintained for 10min under the monitoring of the anaesthetist. Only if there is no new bleeding site, neurosurgeons can start to close.

Neuroendoscope

The patients in this group will receive HE by endoscopic surgery. Well-trained neurosurgeons will make the surgical plan based on the neuronavigational results. The haematomas will be cleared up as much as possible with angled endoscopes following the strategy of 'restricted intracavity operation'. However, some stiffly attached clot should not be removed by force for the avoidance of iatrogenic damage to surrounding brainstem tissue. 'Rebleeding test' will be conducted before close.

Stereotactic aspiration

Patients in this group will undergo HE by stereotactic aspiration. The optimal stereotactic puncture route will be determined by the results of neuronavigation. After puncture needlepoint reaches the centre of the haematoma, the needle will be fixed on the skull. Aspiration of haematoma with a syringe is permitted until first resistance. Urokinase will be administered at least 3 hours after haematoma catheter placement to reduce the possibility of secondary haemorrhage. Multiple doses of urokinase can be injected every 12 hours if CT scan shows residual haematoma exceeding 20% of the initial clot volume.

Study outcomes

Primary outcomes

The primary outcomes in this clinical study are all safety outcomes, including the 30-day mortality, the rate of symptomatic rebleeding at 3 days after surgery and the 30-day rate of bacterial brain infection after surgery.



Secondary outcomes

The secondary outcomes are the following: the rate of haematoma clearance 3 days after surgery, all-cause mortality at 365 days, neurological functional status of 30 days, 90 days, 180 days and 365 days measured by mRS, GCS and GOS. The EGOS, the NIHSS, the EQ-5D-5L will be also assessed for long-term functional evaluation at 180 days and 365 days.

Statistical analysis

The statistical analysis is performed by a biostatistician (HX), while the analysis and interpretation of the results are conducted by a blinded expert. All data analysis is performed using statistical software SPSS V.17. The significance level is determined as $p < 0.05$.

'Intention-to-treat' analysis will be applied in this trial. Categorical analysis of primary and secondary outcomes will be analysed using χ^2 test. The continuous parameters will be analysed using t-test. Survival analysis will be carried out for further comparison of mortality. The subgroups analysis stratified by surgical methods, age (<65 years vs ≥ 65 years), the HV (≤ 10 mL vs > 10 mL), the location (pons vs pons-midbrain vs pons-medulla), the haematoma type (unilateral tegmental vs bilateral tegmental vs basotegmental vs massive type), GCS (5 score vs 6 score vs 7 score), with/without intraventricular haemorrhage and with/without do-not-resuscitate orders is preplanned. Logistic regression will be used to adjust the effect of multivariable.

Patient and public involvement

Patients and the public were not directly involved in the development of the study. However, our investigators discussed the study protocol with relatives of patients.

DISCUSSION

PPH grading scale developed by Huang *et al* represented the latest scoring system in 30-day mortality predictions where GCS score and HV are the two most influential predictors.⁷ In detail, points were assigned as follows: GCS score 3–4 (2 points), GCS score 5–7 (1 point), GCS score 8–15 (0 points); HV > 10 mL, 5–10 mL and < 5 mL was given as 2, 1, 0 point, respectively. Thirty-day mortality rates for patients with the PPH scores of 0, 1, 2, 3 and 4 were 2.7%, 31.6%, 42.7%, 81.8% and 100%, respectively. In STIPE trial, we target critical patients with a score of 2–3 points who may benefit most from surgical management.²

Hydrocephalus after PPH occurred in 30.3% of patients¹⁹ which was identified as an independent prognostic factor of mortality.²⁰ To mitigate the possible impact of hydrocephalus on outcome assessment, we exclude the patients with initial hydrocephalus on admission which needs surgical intervention. However, delayed hydrocephalus may also develop due to brainstem oedema several days after admission both in HE and MT groups.

On that occasion, EVD is allowed to maintain the normal intracranial pressure.

STIPE is the first multi-centre, randomised, controlled, open-label trial to evaluate safety of surgical treatment in patients with PPH in 20 Chinese tertiary hospitals. The trial will provide robust evidence for safety of surgical HE in patients with sPPH.

ETHICS AND DISSEMINATION

The clinical trial must be approved by the ethics committee in all hospitals. All information related to the clinical trial will be fully informed, and patients' family will sign the informed consent before participating in this trial. The results from the clinical trial will be disseminated through academic conferences, and will be published in a peer-reviewed journal.

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Contributors QH, JW, LM, HL, CY and CT were part of designing the trial and approved the final version of the protocol. QH and JW wrote the protocol and LM, HL, CY and CT reviewed the protocol.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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ORCID ID

Qiang He <http://orcid.org/0000-0003-0142-7615>

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