Endoscopic intraventricular hematoma evacuation surgery versus external ventricular drainage for the treatment of patients with moderate to severe intraventricular hemorrhage: a multicenter, randomized, controlled trial

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Study protocol

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Abstract

Background The application of neuroendoscopy in intraventricular hemorrhage (IVH) has attracted more and more attention in recent years. Studies have shown that the use of neuroendoscopy for IVH evacuation has advantages over external ventricular drainage (EVD) alone. However, the cases of most current research are small and all of them are retrospective studies. The aim of this study is to explore the prognosis of patients with moderate to severe IVH who undergo endoscopic IVH evacuation surgery versus those who undergo EVD alone.

Methods The trial is a prospective, randomized, controlled, multi-center clinical trial. Nine hundred and fifty-six subjects with moderate to severe IVH across four tertiary hospitals in China will be randomly assigned (1:1) to receive either endoscopic IVH evacuation surgery or EVD. The primary objective is to compare patients' survival rate at 12 months postoperatively after the two approaches.

Discussion The trial is designed to investigate the prognostic benefits of endoscopic IVH evacuation surgery for patients with moderate to severe IVH. Currently, it has never been investigated in a prospective randomized controlled clinical trial.

Background

Spontaneous intraventricular hemorrhage (IVH) is defined as bleeding into the cerebral ventricular system caused by spontaneous rupture of brain arteries, veins and capillaries instead of trauma. IVH accounts for about 20% of cerebral hemorrhage, but its mortality rate is as high as 50%–80%[1]. According to the results of the STICH trial[2–4], the prognosis of patients with IVH is worse than that of patients without IVH ($p<0.00001$); if patients with IVH have hydrocephalus, the prognosis is the worst.

According to the edition of 2015 Chinese multidisciplinary experts' consensus for spontaneous cerebral hemorrhage diagnosis and treatment and 2015 AHA/ASA spontaneous cerebral hemorrhage diagnosis and treatment guidelines[5], for patients with small amount of IVH without obstructive hydrocephalus, conservative treatment or continuous lumbar drainage can be effective. For patients with large amount of IVH (hematoma occupying more than 50% of the lateral ventricle, secondary obstructive hydrocephalus or obviously increased intracranial pressure), the occupancy effect is dramatic and patients are prone to suffering from hydrocephalus and cerebral palsy, in which circumstances urgent evacuation of hematoma is required, but it is controversial whether it is beneficial for the patients and whether it can improve the prognosis of patients.

As the regular treatment for IVH, external ventricular drainage (EVD) can rapidly reduce intracranial pressure, but clinical practice found that drainage catheters are often blocked by blood clots, and long-term thrombolytic therapy is likely to cause secondary bleeding. Usually, the catheters need to be removed or replaced one week after placement as for the increasing risk of infection.

The application of endoscopy in IVH has attracted more and more attention. Studies have shown that the use of endoscopy for IVH evacuation (with EVD) has advantages over EVD alone[6, 7]. The incidence of postoperative hydrocephalus and the need for ventricular-peritoneal shunt surgery is lower. However, the cases of most current research are small and all of them are retrospective studies. There are no such clinical trials registered at home and abroad, and that is, there is a lack of prospective high-quality clinical studies to further demonstrate the effect of endoscopic treatment for IVH.

Based on this, we intend to conduct a randomized, controlled, multi-center clinical trial to compare the prognosis of patients who undergo endoscopic IVH evacuation surgery versus those who undergo external ventricular drainage for moderate to severe IVH.

Methods

Design

The trial is a prospective, multicenter, randomized controlled trial. A flowchart of the study design was shown in Figure 1. Patients who will receive treatment for IVH would be randomly assigned (1:1) to receive either endoscopic surgery or EVD. The sample size calculation resulted in a requirement of 958 patients. The primary efficacy analysis of overall survival was performed with the logrank test with a significance level of 0.05. Based on previous studies, we assumed a 1-year overall survival rate of 70% in the reference group and planned for the trial to show non-inferiority of new surgical method to the conventional method with a hazard ratio margin of 1.3. With a planned enrollment period of 2 years and a 1-year follow-up phase, and accounting for a potential dropout rate of 5%, we calculated that 958 patients (478 in each group) would need to be enrolled in order to record 456 deaths, which ensured a power of 80%.

Fig 1 A flowchart of the study design.

Patient Recruitment

Patients are screened for eligibility for the trial by their surgeon. Patients aging from 18 to 70 years old with moderate to severe IVH (Graeb score > 4 points) are eligible for this trial. Imaging examination shows deep brain hemorrhage breaking into the ventricles or primary intraventricular hemorrhage, and the amount of bleeding is large, more than 50% of the lateral ventricle or complete ventricle cast.

Patients are excluded from the trial if they have a history of chronic obstructive pulmonary disease, coronary heart disease, chronic kidney disease, blood disorders, cancer, systemic autoimmune disease, or long-term oral corticosteroids. Patients with following conditions are also excluded: imaging examination showing cerebellum and brain stem hemorrhage; detected cerebrovascular diseases in CTA/MRA/MRV/DSA examinations (choose 1 or 2 examinations); ultra-early (within 72 hours) or late enhanced MRI suggesting the presence of brain tumors; history of coagulopathy or long-term oral anticoagulant.

Setting

The study is performed at neurosurgical centers from 4 tertiary hospitals from different parts of China. The organizer will set up an expert panel of 4–6 people to ensure that each participating site has the ability to perform the proper surgical technique.

First, the site applying to participate in the study needs to provide at least two unedited endoscopic IVH evacuation surgery videos and two EVD videos, and provide data of at least 5 cases for endoscopic IVH evacuation surgery and EVD (including preoperative imaging data, surgical records, and postoperative imaging data). The expert panel will judge whether the applicant has the qualification to participate in the study based on the above information.

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist is provided in Additional file1.

Randomization

Weadopt a central randomization method based on the stratification of each clinical trial center, based on the mobile client randomization tool “Randomization Allocation Tool” (RAT) to achieve random assignment of two surgical methods. If the subject is qualified for the trial and signs the informed consent form, the investigator authorized by each center can

input the relevant information of the corresponding subject in the mobile phone client. After the random administrator approves the confirmation, the assigned group is immediately fed back to the researcher's mobile phone, and the researcher performs the prescribed surgical treatment according to the specified group. The method generates a random allocation sequence in advance and can effectively prevent selection bias.

Procedure

The patient in endoscopic group was placed in the supine position and under general anesthesia. Endoscopy was performed using a rigid endoscope (Karl Storz, German). The side with more hemorrhage was taken as the surgical side and a transverse incision of about 3 cm in length was performed 1–2 cm in front of the coronal suture, 2–3 cm beside the midline. Then, a bone window with a diameter of 2–3 cm was made and we cross-incised the dura mater. Next, the surgeons inserted the endoport into the lateral ventricle, which constituted the endoscopic operative channel. The hematoma was removed by a technique using irrigation and aspiration. After exposing the choroid plexus of the lateral ventricle, surgeons should strive to clear the hematoma in the third ventricle through the interventricular orifice. At the same time, the blood clots could be removed with grasping forceps and if there was bleeding, bipolar coagulation could be used to stop bleeding. During the operation, the veins, choroid plexus and ventricular wall should be carefully protected and blood clots that were closely adhering to the choroid plexus were not required to be completely removed. The third ventriculostomy and pellucid septostomy should be performed if possible. The ventricular drainage catheter was placed on the surgical side. The dura and skin were closed in a routine manner. An immediate postoperative CT scan was obtained to assess the residual hematoma. Six hours after surgery, we administered 20,000 U urokinase with 5 ml saline every 8 hours through the catheter and the catheter was closed for 1 hour to allow drug–clot interaction and then reopened to allow for gravitational drainage. Subsequent CT scans were done for any safety concern or every 24 hours. Administration of urokinase was stopped when the CT scans showed that the circulation of cerebrospinal fluid is unobstructed. When CT scans showed that the intracerebral hematoma was significantly reduced and the circulation of cerebrospinal fluid is unobstructed, the catheter could be clamped for 24 h. If there was no acute intracranial pressure increase, the catheter could then be removed.

The patient in EVD group was placed in the supine position and under general anesthesia. The bilateral external ventricular drainage was performed regularly and the unilateral drainage was performed only when one lateral ventricular has little hematoma and the circulation of cerebrospinal fluid is unobstructed. Surgeons usually selected the point 1–2 cm before the coronal suture of the bleeding side and 2–3 cm next to the midline as the puncture point and punctured inwardly along the plane of the puncture point and the line of the ear. The surgeons used a soft catheter with a guide needle to puncture in depth of about 5 cm and then pulled out the guide needle. The next step was to fix the drainage catheter and suture the scalp incision. Postoperative CT was done immediately to confirm positioning of the soft catheter and stability of the hematoma. Six hours or more after catheter placement, we administered 20,000 U urokinase with 5 ml saline every 8 hours and the catheter was closed for 1 hour to allow drug–clot interaction and then reopened to allow for gravitational drainage. Subsequent CT scans were done for any safety concern or every 24 hours. Administration of urokinase was stopped when the CT scans showed that the circulation of cerebrospinal fluid is unobstructed. When CT scans showed that the intracerebral hematoma was significantly reduced and the circulation of cerebrospinal fluid is unobstructed, the catheter could be clamped for 24 h. If there was no acute intracranial pressure increase, the catheter could then be removed.

Outcome Measures

The primary outcome measure is the survival rate of patients at 12 months postoperatively. (Enrollment and assessments in the trial were shown in Table 1)

In addition, secondary outcome measures include treatment-related morbidity, as evaluated by the incidence of:

Postoperative patient survival (OS).

Modified Rankin score (preoperative, one month, three months, six months, 12 months).

Proportion of patients who need ventricular-peritoneal shunt Incidence of postoperative hydrocephalus.

Postoperative intracranial infection.

Hospital stays.

Hospitalization expenses.

Table 1 Enrollment and assessments in the trial

Item	Screening period	Follow-up							
		Operation day	1 day after operation	7 day after operation	2 weeks after operation	1 month after operation	3 months after operation	6 months after operation	12 months after operation
Informed consent	X								
Collect demographic data	X								
Collect medical history	X								
Physical examination	X	X	X	X	X	X	X	X	X
Blood routine examination	X	X	X	X	X	X	X	X	X
Blood biochemical examination	X	X	X	X	X	X	X	X	X
Routine urine test	X		X	X	X	X	X	X	X
Brain CT scan	X	X	X	X	X	X	X	X	X
Brain MRI	X					X	X	X	X
CTA/ MRA/ MRV/ DSA（Choose 1 or 2 items）	X								
HIV、HBV、HCV screening	X								
Graeb score	X	X	X	X	X	X			
Glasgow Coma Scale	X	X	X	X	X	X			
Inclusion/Exclusion criteria	X								
Randomization	X								
Survival rate at 12 months postoperatively									X
Modified Rankin Scale		X	X	X	X	X	X	X	X
Postoperative patient survival (OS)		X	X	X	X	X	X	X	X
Postoperative Complications		☐	☐	☐	☐	☐	☐	☐	☐

Statistical analysis

The OS curves will be estimated using the Kaplan–Meier method. The primary comparison of survival distributions will be performed with the log rank test. Secondary analyses will adjust for prognostic factors using appropriate regression

models (e.g., Cox proportional hazards model). All measures of efficacy will be compared by an intention-to-treat analysis including all randomized patients.

Continuous variables will be assessed for normality and equality of variances between groups. Discrete variables will be summarized by frequencies/proportions. For continuous variables, analysis of variance and/or regression will be used, where appropriate. If assumptions for these tests are violated, alternative nonparametric tests will be used. Difference between groups with respect to discrete variables will be evaluated by using c2 tests.

Discussion

Our trial is a randomized controlled trial designed for patients with moderate to severe IVH. It compares a relatively new surgical procedure (endoscopic IVH evacuation surgery) with the current standard treatment (EVD). As with all surgical clinical trials, timing of the trial is crucial. If the trial is conducted too early, the new technique may still undergo too many modifications to allow application of a standardized procedure. In addition, recruitment might be too slow and the trial might turn out to be unfeasible. In contrast, if the trial is left too late, the new technique may become part of the mainstream treatment without adequate proof of its equivalence. In that case, too many patients might refuse randomization and the trial could also become unfeasible. Currently, the interest among endoscopy is strong and investigators are eager to enroll patients.

In summary, the available evidence suggests that endoscopic IVH evacuation surgery may be a valid alternative surgery to EVD with equal OS for patients diagnosed with moderate to severe IVH. This trial is aimed to provide high-quality evidence to support this hypothesis.

Trial Status

The trial was reregistered on July 25, 2019 at ClinicalTrials.gov Patient and recruitment will begin in 2019. The programmed completion date for the recruitment was September 31, 2022. The trial is now in the recruitment stage of data. The protocol version number is V2.0 (April 23, 2019).

Abbreviations

IVH: intraventricular hemorrhage; EVD: external ventricular drainage; STICH: Surgical Trial in Intracerebral Haemorrhage; AHA/ASA: American Heart Association/American Stroke Association; CTA/MRA/MRV/DSA: computed tomography angiography/magnetic resonance angiography/ magnetic resonance venogram/digital subtraction angiography; SPIRIT: The Standard Protocol Items: Recommendations for Interventional Trials; RAT: Randomization Allocation Tool; CT: computed tomography; OS: Postoperative patient survival.

Declarations

Acknowledgements

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Authors' contributions

ZJ and MC designed the protocol. LY is responsible for data management and statistical analyses. CZ, YJ, CX is responsible for quality control. ZJ drafted the first study protocol. MC, TC is responsible for contacting the other subcenter

directors and recruiting patients. All authors read and approved the manuscript.

Funding

The trial is supported by Institute of Neurosurgery, Jinling Hospital. The funding body participates in the design of the study and is responsible for the collection of the data and writing the manuscript.

Availability of data and materials

The data are currently unavailable.

Ethics approval and consent to participate

Central ethical approval has been confirmed from the Ethical Institutional Review Board of Jinling Hospital (ref. approval no. 2019NZKY–014–01) and recruitment will not begin at other centers in the trial until local ethical approval has been obtained. Informed consent will be obtained from all patients or their guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

SPIRIT Figure.

Item	Screening period	Follow-up							
		Operation day	1 day after operation	7 day after operation	2 weeks after operation	1 month after operation	3 months after operation	6 months after operation	12 months after operation
Informed consent	X								
Collect demographic data	X								
Collect medical history	X								
Physical examination	X	X	X	X	X	X	X	X	X
Blood routine examination	X	X	X	X	X	X	X	X	X
Blood biochemical examination	X	X	X	X	X	X	X	X	X
Routine urine test	X		X	X	X	X	X	X	X
Brain CT scan	X	X	X	X	X	X	X	X	X
Brain MRI	X					X	X	X	X
CTA/ MRA/ MRV/ DSA（Choose 1 or 2 items）	X								
HIV、HBV、HCV screening	X								
Graeb score	X	X	X	X	X	X			
Glasgow Coma Scale	X	X	X	X	X	X			
Inclusion/Exclusion criteria	X								
Randomization	X								
Survival rate at 12 months postoperatively									X
Modified Rankin Scale		X	X	X	X	X	X	X	X
Postoperative patient survival (OS)		X	X	X	X	X	X	X	X

Figures

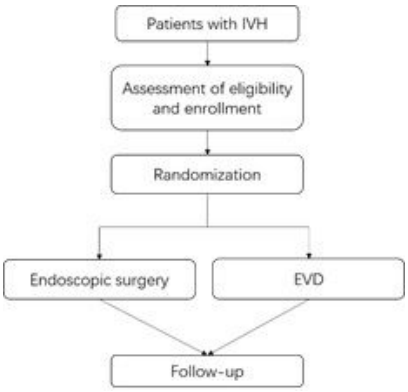

Figure 1

A flowchart of the study design.