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Safety and efficacy of endovascular therapy and gamma knife surgery for brain arteriovenous malformations in China: Study protocol for an observational clinical trial

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ABSTRACT

Introduction: Brain arteriovenous malformations (BAVMs) are associated with high morbidity and mortality. The treatment of BAVM remains controversial. Microinvasive treatment, including endovascular therapy and gamma knife surgery, has been the first choice in many conditions. However, the overall clinical outcome of microinvasive treatment remains unknown and a prospective trial is needed.

Methods: This is a prospective, non-randomized, and multicenter observational registry clinical trial to evaluate the safety and efficacy of microinvasive treatment for BAVMs. The study will require up to 400 patients in approximately 12 or more centers in China, followed for 2 years. Main subjects of this study are BAVM patients underwent endovascular therapy and/or gamma knife surgery. The trial will not affect the choice of treatment modality. The primary outcomes are perioperative complications (safety), and postoperative hemorrhage incidence rate and complete occlusion rate (efficacy). Secondary outcomes are elimination of hemorrhage risk factors (coexisting aneurysms and arteriovenous fistula), volume reduction and remission of symptoms. Safety and efficacy of endovascular therapy, gamma knife surgery, and various combination modes of the two modalities will be compared. Operative complications and outcomes at pretreatment, post-treatment, at discharge and at 3 months, 6 months and 2 years follow-up intervals will be analyzed using the modified Rankin Scale (mRS).

Discussion: The most confusion on BAVM treatment is whether to choose interventional therapy or medical therapy, and the choice of interventional therapy modes. This study will provide evidence for evaluating the safety and efficacy of microinvasive treatment in China, to characterize the microinvasive treatment strategy for BAVMs.

1. Introduction

Brain arteriovenous malformation (BAVM), with an incidence of 1.12–1.42 cases per 100,000 person years, is a complex of abnormal arteries and veins that directly fistulize without an intervening capillary bed [1,2]. Hemorrhage is the most common presentation, occurring in 40–50% patients at initial diagnosis. The annual risk of hemorrhage ranges from 1.3% to 4%. The second most common presentation is seizure, occurring in 20–30% of patients, followed by headaches (5%–14%) and focal neurological deficits (around 5%) [3–6]. The management of BAVM is controversial and complex. Three current treatment modalities are surgical resection, endovascular embolization and stereotactic radiotherapy (Gamma knife surgery). They are used alone or in various combinations depending on local expertise, BAVM architecture, and clinical presentation [7]. A randomized trial of unruptured brain arteriovenous malformation (ARUBA) showed that medical management alone is superior to medical management with interventional therapy for the prevention of death or stroke in patients with unruptured BAVMs [8]. However, case-selection bias and short-term follow-up are remaining controversies of this study [9,10].

Abbreviations: BAVMs, Brain arteriovenous malformations; REAL-CHINA, Registry of endovascular therapy and Gamma knife surgery for brain Arteriovenous Malformation in China; ChiCTR, Chinese Clinical Trial Registry; ICH, Intracerebral hemorrhage; SPIRIT, Recommendations for Interventional Trials; PRC, People's Republic of China; FDA, Food and Drug Administration; CRF, Case report form; CT, Computed tomography; mRS, modified Ranking Scale; SAE, Serious adverse event; SM, Spetzler Martin grade

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The goal of BAVM treatment is to eliminate intracerebral hemorrhage (ICH) risk and to preserve neurological functions of the patient. Microsurgical resection of BAVMs in certain locations with a large nidus, eloquent cortex, deep draining veins, or high-flow shunts may carry a relatively high risk of morbidity [11,12]. Microinvasive treatment (Endovascular therapy and Gamma knife surgery) is increasingly used for the management of non-surgical BAVMs, especially for lesions that are deep, in eloquent locations, inaccessible or less safely accessible to surgical. They represent a safe and efficacious primary treatment option [13]. Combining endovascular embolization with gamma knife to treat BAVM allowed potential volume reduction and elimination of high-risk features [13–16].

The overall BAVM embolization complication rates of approximately 5%–15% have been reported. Recent studies have found a permanent morbidity rate of 3–14% and a mortality rate of 0–4% [17,18]. Several authors have reported that the complete cure of BAVMs by microinvasive treatment is approximately 20% of all BAVMs irrespective of their angioarchitecture [19–21]. However, There is a lack of data from prospective, multicenter observational clinical trials to settle the following questions on current microinvasive treatment for BAVMs: 1. The overall procedural and clinical complication rate, morbidity and mortality rate of microinvasive treatment. 2. The complete occlusion rate, and appropriate number of embolization or stereotactic radiotherapy sessions considering angioarchitectural characteristics. 3. The postoperative hemorrhage incidence rate during the session intervals until complete obliteration occurs.

REAL-CHINA is a study aims to address these above questions. The first primary objective is to observe the safety of current microinvasive treatment through operative complications, including procedural complications and clinical complications, and clinical outcomes. The second primary objective is to observe the efficacy of microinvasive treatment through postoperative hemorrhage incidence rate and complete occlusion rate. The secondary outcomes are: a. elimination of hemorrhage risk factors (coexisting aneurysms and arteriovenous fistula); b. volume reduction; c. remission of symptoms. The results of this study will provide strong evidence regarding the safety and efficacy of microinvasive treatment as an intervention to BAVM patients.

2. Methods and analysis

2.1. Trial design

This is a prospective, non-randomized, and multicenter observational registry clinical trial, focusing on complications and patients outcomes of microinvasive treatment. This study has followed the Standardized Protocol Interventions: Recommendations for Interventional Trials (SPIRIT) 2013 Statement, which defined standard protocol items for clinical trials [22]. The complete protocol is available at www.chictr.org.cn. The study protocol is performed at Beijing Tiantan Hospital, Capital medical university (China National Clinical Research Center for Neurological Diseases), which is the largest neurosurgical center in China. The trial was registered on 7 June 2016 at Chinese Clinical Trial Registry (ChiCTR): ChiCTR-PON-16008608.

The treatment of AVM is controversial, especially for unruptured AVMs and AVMs eligible to various modalities. This trial will include both ruptured and unruptured AVM patients. Most ruptured AVM patients should be treated and the modality is based on clinical state and architectural characteristics. So we think it will be ethically illegal to randomize. For microinvasive eligible patients, some patients may be more eligible to endovascular therapy, some to gamma knife surgery, and some to combinations of the two modalities. We will make individualized strategies for each to achieve the lowest risks and highest benefits. Considering the controversy in the treatment of AVM, we think we should not randomize this trial for ethical reasons. We aim to observe the current safety and efficacy of microinvasive modalities, which we hope could guide clinical practice method and direction in the future.

2.2. Patients

BAVM patients diagnosed at a participating clinical centers and patients for whom endovascular therapy and/or gamma knife surgery were preferred as the primary treatment modalities will be candidates for this study. The modality of treatment is based on integrated analysis of clinical neurosurgeon, neurointerventional surgeon and radiologist. Trial will be explained to all participants before involvement. The participation of this study is voluntary and patients have the right to withdraw at any point in time and to ask any questions. The first patient was recruited on 1st August 2016.

2.3. Inclusion criteria and exclusion criteria

2.3.1. Inclusion criteria

1 BAVM patients based on clinical and imaging evaluation
2 Patients between 12 and 60 years old
3 Endovascular therapy and/or gamma knife surgery are/is preferred as primary treatment strategy
4 Patients agree to participate in this study and sign informed consent

2.3.2. Exclusion criteria

1 Patients with a history of microsurgery resection of BAVM
2 Acute stage of ICH: supratentorial > 30 ml; Infratentorial > 10 ml; mRS > 3
3 Uncontrolled hypertension or diabetes
4 Liver and/or renal dysfunction
5 Contrast allergy or other angiography contraindications
6 Positive pregnancy test
7 Other contraindications of surgery
8 Refuse to participate

2.4. Participating centers

The trial is taking place in People's Republic of China (PRC). Participating centers spread all over China and are representative centers of their region. Participating centers can provide multidisciplinary and multimodality care for BAVM patients. Considering the low incidence (1.12–1.42/100000 patient-years) of this disease [1,2], there is no requirement for a minimal number of procedures. It will be conducted in at least 12 centers: 1. Beijing Tiantan Hospital, Capital Medical University (Organizer); 2. The Affiliated Hospital of Qingdao University; 3. The First People's Hospital of Lianyungang; 4. The First Hospital of Shijiazhuang; 5. The First Hospital of Fangshan District, Beijing; 6. The First Affiliated Hospital of Jinzhou Medical University; 7. The Civil Aviation General Hospital; 8. Peking University International Hospital; 9. Inner Mongolia People's Hospital; 10. Xinjiang Uygur Autonomous Region People's Hospital; 11. The First Affiliated Hospital of Anhui Medical University; 12. The Hospital of Heilongjiang Province.

2.5. Study interventions

Interventional therapies consist of current endovascular therapy using n-butyl cyanoacrylate (NBCA), ONYX or detachable coils, and gamma knife surgery. Two modalities are performed alone or in combination. Interventions are applied flexibly as in normal practice. The predefined route of this study is demonstrated in Fig. 1. We will organize regular training sessions to standardize the treatment option as much as possible.

Most common combination modes of endovascular therapy and gamma knife surgery including:

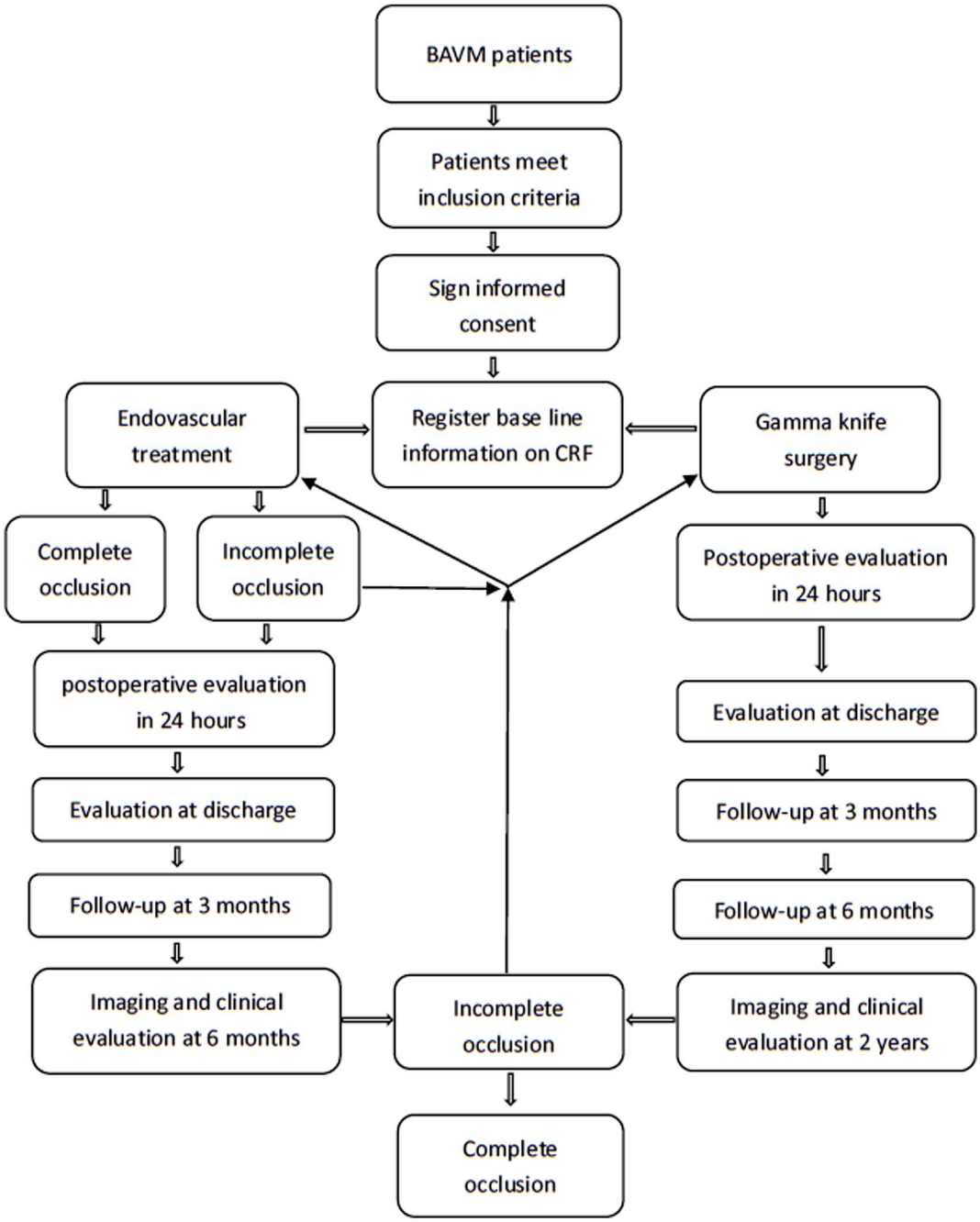

Fig. 1. Diagram of this study protocol. BAVM: Brain arteriovenous malformation; CRF: Case report form.

1 Endovascular therapy only
2 Gamma knife surgery only
3 Endovascular therapy + gamma knife surgery
4 Gamma knife surgery + Endovascular therapy
5 Gamma knife surgery + Endovascular therapy + Gamma knife surgery
6 Endovascular therapy + Gamma knife sugery + Endovascular therapy

For patients who are eligible for endovascular therapy and/or gamma knife surgery, the selection of treatment modality is mainly based on the existence or not of the following risk factors: initial hemorrhage presentation, nidus > 3 cm, eloquent area, coexisting aneurysms, coexisting arteriovenous fistula, microcatheter accessibility and drainage dilation, etc. The option is based on objective comparison of embolization risks and hemorrhage risks after gamma knife surgery (before complete occlusion). For patients with initial hemorrhage presentation, coexisting aneurysms, coexisting arteriovenous fistula and drainage dilation, endovascular embolization is prior to gamma knife surgery. For patients with nidus ≤ 3 cm, eloquent area and no initial hemorrhage presentation, we are inclined to perform gamma knife surgery. For patients with nidus > 3 cm, a combination of the two modalities will be performed unless complete occlusion is achieved by embolization. If the feeding articles are microcatheter inaccessible, gamma knife surgery will be recommended. A personalized treatment plan will be made by our team for each patient based on, but not confined to the above characteristics.

Endovascular therapy may include BAVM embolization, or coiling of BAVM associated aneurysms. The embolization materials used will be limited to those agents approved by the Food and Drug Administration (FDA) or by the approval agency applicable to China. This plan allows for the introduction of new agents during the course of

the study. The name of the agent and the frequency of use will be recorded on the case report form (CRF).

Gamma knife surgery involves the targeting of the BAVM nidus and adjacent vessels, intended to induce a reduction in nidus size, and possible obliteration of the BAVM. Based on local patterns of practice, acceptable variations exist in the type of equipment used, the methods of measurement used to assess the location and size of the BAVM chosen for therapy, the individual doses and numbers of treatments. The modality, energy, collimator size, prescription and duration of treatment will be recorded on the CRF.

2.6. Outcome measures

The first primary outcome of the study is the overall complications, morbidity and mortality of microinvasive treatment. The complication incidence rate will also be compared between different combination modes (e.g. endovascular embolization alone, gamma knife surgery alone and combination of endovascular therapy and gamma knife surgery). The second primary outcome is postoperative ICH incidence rate and complete occlusion rate. ICH is defined as a clinically symptomatic event (sudden-onset headache, seizure, focal deficit, or a combination of these features) with signs of fresh bleeding on computed tomography (CT). The secondary outcomes are: a. elimination of hemorrhage risk factors (aneurysms and arteriovenous fistula); b. volume reduction; c. remission of symptoms. Patient neurological function and outcomes at pretreatment, post-treatment, at discharge and at 3 months, 6 months and 2 years follow-up are measured using the modified Ranking Scale (mRS) [23]. An mRS of 0–2 is identified as a favorable outcome, and a score of mRS ≥ 3 is defined as an unfavorable outcome.

2.7. Sample size estimation

Previous studies have proved higher total obliteration rate and lower complication rate with the combination of endovascular therapy and gamma knife surgery, than that of endovascular therapy along. According to the literature [13,24,25] and our experiences [26–28], we hypothesize that the overall complication rate in the endovascular therapy group is 15%, and that of combined endovascular therapy and gamma knife group is 5%. The total obliteration rate of endovascular therapy group is 20%, and that of combined endovascular therapy and gamma knife group is 35%. Considering the multiplicity of clinical outcomes. We estimate sample size respectively. For the complication, setting alpha at 0.05 and beta at 0.1. Sample size ratio is 1:1. Considering 10% loss to follow-up, the total sample size needed to detect this difference is 400 patients. For total obliteration, at the same parameters, the total sample size needed to detect this difference is 326 [29]. The patients in the former will cover all the patients in the later. So the final sample size for this study is 400 patients.

2.8. Data collection and planned patient follow-up

Data are prospectively collected using paper CRF, as well as electronic CRF simultaneously through a study website using a login and password (Res Man Research Manager). All patients will accept in person follow-up at the time of standard clinical visits or structured telephone follow-up before procedure, within 24 h after procedure, at discharge, and at 3 months, 6 months and 2 years intervals (Table 1). Complications related to operation, neurological conditions and ICH will be carefully monitored during the whole period of follow-up. These intervals will serve to determine mRS scores, and to inquire about possible neurological events and hospital admissions. We will compare the outcome of patients at different visits. Patients are followed up with digital subtraction angiography (DSA) at the last treatment session, to prove definite eradication of the lesion. There is no extra test, risk or cost beyond what is considered normal care in this study.

Table 1
Flow diagram of the patient evaluation.

Items	First visit preoperative	Second visit 24 h postoperative	Third visit discharge	Forth visit 3 months	Fifth visit 6 months or 2 years[a]
Demographics	✓				
History	✓				
Medication	✓	✓	✓	✓	✓
Informed consent	✓				
Imaging	✓				✓
Angioarchitecture	✓	✓			✓
Procedure details		✓			
Complications		✓			
Hemorrhage during follow-up				✓	✓
mRS	✓	✓	✓	✓	✓
SAE		✓	✓	✓	✓
Subsequent treatment				✓	✓

mRS: modified Rankin Scale; SAE: Serious Adverse Event.
[a] For patients underwent endovascular therapy only, the last follow-up will be at 6 months. For patients underwent gamma knife surgery, the last follow-up will be at 2 years.

2.9. Data analysis

Standard statistical techniques will be used to describe patients' characteristic. The overall primary and secondary outcome incidence rate of all subjects will be analyzed. The primary and secondary outcome incidence rate of patients received different combination modes will also be analyzed and compared. Factors associated with primary and secondary outcomes will be analyzed based on the following subgroups. Coefficient weighting method will be used considering the various number of cases form different centers.

Primary outcome

1 Complications: Yes or No
2 Complete Occlusion: Yes or No
3 Postoperative ICH during follow-up: Yes or No

Secondary outcome

4 Elimination of risk factors: Yes or No
5 Volume reduction > 50% > Yes or No
6 Remission of symptoms: Yes or No

All statistical analyses will be conducted using SPSS 18.0 (Chicago, IL). Continuous variables will include the number of subjects, means, standard deviations, medians, minima and maxima. Categorical variables will include frequencies and percentages. Continuous variables will be compared between groups using Student *t*-test. Categorical variables will be compared using Fisher exact test or the Pearson χ^2 test. Univariate and multivariate logistic analyses will be done to assess factors on embolization complications. (2-tailed, $P < 0.05$ was considered significant) Free-hemorrhage survival time will be analyzed using Kaplan-Meier survival analysis.

3. Discussion

The innovation point of this study is comprehensive assessment of microinvasive treatment for BVAM through an observational trial. The most confusion on BAVM treatment is whether to choose interventional therapy or medical therapy, and the choice of interventional therapy modes. Microinvasive treatment could increase the safety of interventional surgeries for ruptured or unruptured BAVMs which are

inaccessible to microneurosurgery, high Spetzler Martin(SM) grade and eloquence in location [13]. We hope to accelerate development of this field by performing the rigorous clinical trial focusing on complications, morbidity and mortality, complete occlusion rate, and postoperative hemorrhage rate. Besides this, we will perform internal comparison in terms of clinical outcomes. Subgroups for internal comparison include patients underwent endovascular therapy only, patients underwent gamma knife only, and patients underwent different combination modes of endovascular therapy and gamma knife surgery. The secondary outcomes such as elimination of risk factors (coexisting aneurysms and arteriovenous fistula), volume reduction, and remission of symptoms will also be analyzed in all subjects and subgroups. This study is feasible in terms of patient acquisition, operative intervention, supervision and patient evaluation. This result of this study could make us more clearly in understanding microinvasive treatment for BAVM in terms of safety and efficacy.

During the whole process of this study, we should pay more attention to patients follow-up. We will register multiple and detailed contact information of each patient. Some reasonable preferential aid in terms of finance, care and consultation will also be provided for patients in need. We will remind them of regular and normal examination (MRA, DSA) and treatment (more sessions). Dropping out of the intervention program may be due to personal, familial or other reasons that may prohibit them from continuing the study. We accounted for the dropout rate in the sample size estimation to ensure that we could reach sufficient power for the study.

3.1. Trial monitoring

A trained research assistant will manually enter the data into an electronic database. A second research assistant independent from this study will check the quality and accuracy. The monthly auditing, data quality and statistical analysis are managed by a third party who shall be responsible for notifying the principal investigator and Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University of any issues that arise. Any unanticipated adverse events or serious adverse event (SAE) that occur during the course of the study will be reported to the Institutional Board.

3.2. Ethics and dissemination

The study has been evaluated and approved by the ethics community of Beijing Tiantan Hospital, Capital Medical University, and ethics community of sub-centers. Grant number: KY2016-025-02. This study is in accordance with good clinical practice and ethical principles described in the Declaration of Helsinki. All participants and/or their family members will provide written informed consent. The result of the study will be published on peer-review journals. For any revised study procedure, the modification will be submitted to the Institutional Board for approval. The data will be kept confidential with only limited access to research investigators and related research assistants.

3.3. Trial status

The trial has started to recruite patients since August 2016. We will continue to recruit until the sample size of 400 participants is reached. The trial is expected to report its main outcomes in 2019.

Authors' contributions

LY, JY and HX conceived and designed the study protocol and developed the intervention programs. JH and LX drafted and finalized the manuscript. All authors have approved the final manuscript.

Trial registration

Publicly entitled as: Registry of endovascular therapy and Gamma knife surgery for brain Arteriovenous Malformation in China (REAL-CHINA). Chinese Clinical Trial Registry (ChiCTR): ChiCTR-PON-16008608, registered on 7 June 2016.

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Competing interests

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.conctc.2017.06.006.

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