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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: