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Keywords:	Un-ruptured aneurysms, Interventional treatment, Craniotomy, Prospective

The China intracranial aneurysm project (CIAP): A prospective cohort study of interventional treatment and craniotomy for un-ruptured aneurysms

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ABSTRACT

Introduction: Intracranial aneurysm (IA) is a complex condition with serious side effects. There are two approaches for the treatment of IA: interventional therapy and craniotomy, each have their advantages and disadvantages in terms of treatment efficacy. To avoid the over-treatment of un-ruptured aneurysms（UIA）, save valuable medical resources, and reduce patient mortality and disability rate, it is vital that neurosurgeons select the most appropriate type of treatment to provide the best levels of care. However, making this clinical decision is difficult. Here, we propose a refined prospective, multicenter study for the Chinese population with strictly defined patient inclusion criteria, along with the selection of representative clinical participating centers.

Methods and analysis: This is a multicenter, prospective cohort study. Since the incidence of IA is very dangerous and ethical issues need to be taken into account, researchers are not able to use randomized controlled trials. The proposed study will be carried out by 12 clinical centers located in different regions of China. The trial recruitment programme begins in 2016 and is scheduled to be complete in 2020. We expect 1500 subjects with UIA to be included. Clinical information relating to the subjects will recorded objectively. The main endpoints are an evaluation of the safety, efficiency and economic benefits of interventional treatment and craniotomy for 6 months after surgery, with each participant completing at least one year of follow-up.

Ethics and dissemination: The research protocol and the informed consent form (ICF) for participants in this study are supported by the ethics committee of Zhujiang Hospital of Southern Medical University (2017-SJWK-001).

Clinical Trials registration number: NTC03133598

Keywords: Un-ruptured aneurysms; Interventional treatment; Craniotomy; Prospective

Strengths and limitations of this study

1. This represents the first prospective cohort study to provide strategies for the selection of treatment options for aneurysm in China, including a number of clinical centers throughout the country, thus fully representing the Chinese population.
2. Inclusion criteria and exclusion criteria are in line with foreign research programs, but have been combined with China's national conditions to formulate a reasonable research plan, which incorporates an adequate sample size but ensures that the study can be completed on time.
3. The research process will be coordinated by several departments to ensure the quality and reliability of research data.
4. The only limitation of the proposed study is that it may include multiple forms of clinical data, which may differ from the intended purpose due to human subjectivity.

INTRODUCTION

IA is a common cause of subarachnoid hemorrhage (SAH) and is estimated to affect between 0.2% and 9% of the population. While the detection rate for un-ruptured IAs (UIAs) in healthy people can be as high as 3%, these detection rates differ across different countries.[1] According to recent research, the overall prevalence of UIA is 7.0% in Chinese adults aged 35 to 75 years, with women more affected than men (8.4% versus 5.5%, respectively).[2] In the case of un-ruptured cerebral aneurysms (UCAS), the natural course of UIA varies according to the size, location, and shape of the aneurysm.[3] Interventional therapy and craniotomy represent the two main methods for treating UIAs. However, despite our current knowledge of UIA, and even when we take into account information relating to pathological, radiological, and clinical studies, there is still no specific criteria that can be used select the appropriate treatment strategy. Consequently, there is an urgent global requirement to develop methods which will help in selecting the most appropriate treatment for UIA.[4]

A large number of researchers have investigated the treatment options available for IA and many of these studies indicated that the postoperative complications associated with interventional therapy are lower than those of craniotomy. However, the short and long-term occlusion rate was lower for interventional therapy than for craniotomy. These previous studies have also highlighted that the size and anatomical location of aneurysms can exert a significant influence on the effect of treatment.[5-9] Interestingly, research failed to identify any significant difference in costs when treatment was compared between endovascular and neurosurgical approaches over the short term.[10] The International Subarachnoid Aneurysm Trial (ISAT) further showed that compared with craniotomy, interventional treatment can clearly improve patient outcome; however, most of the participants in this study had small aneurysms. Consequently, this trial could not definitively conclude that coiling is safer than clipping for all cases of IA.[11-14] While controversial, the ISAT did provide us with some degree of understanding of IA.[15 16]

Previous research has also shown that the risk of IA rupture is 1% to 2%, and leads to intracranial hemorrhage, a dangerous condition which is associated with a high mortality and disability rate.[17] However, while UIAs do not generally rupture during long-term follow-up, some medical treatment can increase bleeding rate and the rate of rupture. Thus, in the absence of any specific guidelines for the treatment of aneurysms, the aim of this study was to assess the safety, efficacy and economic benefits of interventional treatment versus craniotomy, and propose a scientific strategy for selecting the appropriate form of surgical treatment for UIA, which could be deployed across clinics worldwide.

METHODS AND ANALYSIS

Study design

CIAP is an ongoing, multicenter trial supported by the National Key Research

Development Program, and predominantly studies aneurysms from 5 different aspects: 1) The risk of antithrombotic therapy in patients with UIAs complicated by ischemic cardio cerebrovascular diseases; 2) The rate of rupture; 3) The risk of rupture and developing a model to predict rupture; 4) Treatment options for UIAs and 5) The development of standardized treatments for early stage UIA bleeding; this study is one of the sub-topics, is an observational study.

This study evaluates the treatment options for UIAs from the point of view of safety, efficacy and economic benefits, and compares these factors between interventional therapy and craniotomy. The incidence of aneurysms is relatively high among the population, and China is a large country with a wide population distribution. Thus, in order to fully reflect the population more objectively, the researchers using multicenter, prospective cohort study to complete this study, which will last for five continuous years continuously. Furthermore, refer to previous research studies and take into account the characteristics and hazards of UIA，the researchers does not involve random division of subjects into groups3 and 1500 UIA subjects are expected to be included. Each subject will be followed up at fixed time points by researchers and the normal procedures of treatment would not be affected by subjects joining the CIAP study. All follow-up data, and other clinical information, relating to the subjects are recorded in detail, and data is analyzed statistically. A concise flow chart of the entire study is shown in Figure 1. The study protocol was approved by the Ethics Committee of Zhujiang Hospital of Southern Medical University (Reference Number: 2017-SJWK-001) and its respective Institutional Review Board (IRB). The trial has been registered at ClinicalTrials.gov with reference number NTC03133598.

Participation center qualification

In order to evaluate UIA treatment objectively, it is important to avoid subject bias and ensure that an adequate number of cases are included in the study. The researchers selected 12 clinical centers (each center covering more than 2 community or referral units) to conduct this study in collaboration which distributed across several regions of China (south east, southwest, northwest, northeast). According to an incomplete dataset; in 2015, a total of 6000 IA patients had been evaluated across the 12 clinical centers. Consequently, we believe that each center can adequately represent the real level of IA diagnosis and treatment at a regional and national level. The12 clinical centers are therefore representative.

There are no specific guidelines for the treatment of UIA. As such, differences exist in the diagnosis and treatment of IA across different regions, different centers, and even between different neurosurgeons. in this study, the basic requirement of neurosurgeons who performs surgery on subjects is able to complete the aneurysm surgery more than 30 cases per year independently. The study also features an imaging interpretation center (Internationally Recognized Image Interpretation Laboratory, established by Xuanwu Hospital and Image Center of the University of California, Los Angeles, UCLA); this center is responsible for the unified standard

interpretation of imaging data arising from the 12 clinical centers.

Subjects selection and screening

The purpose of this study is to recruit patients who are suffering IA without rupture. First, subjects are diagnosed with UIA, either by computed tomography angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA). Patients with fusiform, traumatic, bacterial or dissecting aneurysms, or with SAH of unknown origin, are excluded. These types of patients, involving other vascular diseases (arteriovenous malformation [AVM], arteriovenous fistula [AVF]), malignant tumors, or poor physical condition factors are expected to live for less than a year, therefore, all not suitable for study. In order not to disturb the objectivity of the study and provide good opportunities for follow-up, the researchers also emphasized the ability of subjects to live independently (using the modified Rankin scale (mRS) and included those with a score of $\leqslant$3). Patients were also excluded if they were unable to communicate normally due to serious mental illness; the size of the aneurysm was less than 3 mm; the diagnosis of aneurysms is unclear or difficult. The specific inclusion and exclusion criteria for the trial are provided in Table 1 and Table 2, respectively.

The study involves twelve recruiting centers, each of which requiring IRB approval before recruiting cases. Patients diagnosed with UIA not only receive formal diagnosis and treatment for their aneurysms, but also, along with their families, receive full communication from the researchers, with regard to the aims of the study. Patients can then voluntarily join the study and sign the ICF. Once this is done, the subject's imaging data will be transmitted to the imaging interpretation center to re-confirm the diagnosis. If the two diagnoses are not consistent, then the subject is excluded. The subjects can withdraw from the study at any time, and the researchers can determine whether the subjects continue the study according to their physical status. When serious adverse events occur during the course of the trial, the researchers must terminate the study in advance and report to the ethics committee; adverse events are also entered into the case report form (CRF). This study is an observational study that does not interfere with the normal course of clinical diagnosis and treatment; even if subjects withdraw from the study, it would not affect their treatment.

Data collection

Once subjects are included in the study, all information about the course of diagnosis and treatment are recorded in the CRF. This study also uses an electronic data collection system (EDC) developed by the National Center for Cardiovascular Disease; information stored on CRFs are entered into the EDC by a designated person on each site, and each site shares data with the EDC. The objective of this study was to objectively compare the safety, efficacy and economic benefits of the two treatment methods for UIA, and each subject followed for at least one year (at 3, 6, and 12 months), follow-up data were acquired by a neurosurgeon either by telephone or by

social tools as soon as possible. In most cases, DSA examination should be carried out six months after the operation to confirm the effect of treatment, which is the vital end point of this study, data acquired at three and twelve months after surgery are also an important aspect of the study. A detailed follow-up plan is given in Figure 2. During the study, the researchers were obliged to protect the personal privacy and medical information of each subject, and strictly adhere to ethical guidelines.

Data management

As all data will be collected using CRFs and the EDC, the CIAP have established a data management committee (DMC, located in Xuanwu hospital) to supervise data quality, and hired a special data management company responsible for constructing the EDC and ensuring data security, integrity and accuracy. Before the subjects are formally enrolled, the DMC holding CRF and EDC data entry study classes for main researches in each collaboration clinical center; considers data entry, modification and retrieval, and sets permissions for the main researchers in the EDC. A clinical research operator (CRO) supervises project progress and quality of data implementation, and the researcher assigned, the clinical research associate (CRA) regularly visits each participating center to ensure that all contents of the research program are strictly adhered to; if not, the CRA promptly submits information to the investigators. Throughout the project, a research summary conference will be held every 6 months, to discuss progress and solve any problems that may arise.

Data analysis

The Department of Medical Statistics at the National Center for Cardiovascular Diseases is responsible for all data management and statistical analysis. SPSS V21.0 statistical software (IBM Corp, Armonk, New York, USA) is used to analyze the results, with normally distributed data represented by ±SD. Skewed distribution data is described by the median (M) and the four quartile range (P25; P75), using an independent t test or rank sum test. Categorical variables are described by frequency and percentage and grouped data, rate or percentages between the groups are compared with the Chi square test or Fisher exact test. Rank data is analyzed by the rank sum test. $P<0.05$ was considered to indicate statistical significance.

DISCUSSION

To our best knowledge, CIAP is the first project to explore the characteristics of Chinese intracranial aneurysms within the nation of Chinese people, and does so from a range of different aspects: the rate of spontaneous aneurysm rupture; risk factors of rupture; and the emergency treatment required for ruptured aneurysms; etc., in particular, the study compares two different treatment methods for UIA. IA is a common cause of SAH, but this does not mean that the SAH rate is high so that the incidence of IA is also high,[18] SAH can lead to an erroneous understanding of IA to a certain extent. Consequently, we should exclude the unknown causes of SAH.[19] DSA has traditionally been considered the gold standard for detecting aneurysms. However, combined with existing data, indicates that the incidence of UIA within the population

varies according to the method of examination, the main reason for this is that the accuracy of different diagnostic methods is affected by the size of aneurysms. Studies have shown that the sensitivity of DSA is only 85% for small aneurysms (<3 mm), and that the efficacy of computed tomographic (CT) angiography for diagnosing intracranial aneurysms is increasingly being recognized,[1 20-23] this study excludes patients with small aneurysms, and in doing so, increases the accuracy of the study. This, however, means that the study can be considered as incomplete as it only targets aneurysms of a certain size.

The treatment of IA cannot be separated from interventional treatment and craniotomy. Interventional therapy is becoming more and more popular among neurosurgeons, but selecting which of the two approaches to use for treatment has been controversial.[24-26] Most scholars believe that interventional therapy is associated with lower mortality compared with craniotomy, that the recurrence and re-bleeding rate of interventional therapy is higher,[12] and combined with other techniques may achieve better results.[5 27 28] The recurrence rate of interventional therapy is higher because for certain types of aneurysms, such as wide neck aneurysms, the treatment effect is not satisfactory. However, as the intervention materials and technology improves, many scholars have adopted this approach for the treatment of aneurysms and have obtained good results. [29-33] Comparing the two methods in terms of safety and effectiveness, it is necessary to consider a range of factors, such as age, gender, subarachnoid hemorrhage and aneurysm size; this is because these are the principal factors which can influence the re-bleeding of aneurysms.[34 35] Surgery can cause hemodynamic changes of an aneurysm, but there is no conclusive evidence to show that this plays a positive role in the recurrence of aneurysms, the study does not take into account the effects of hemodynamics on the results,[36 37] rather, the researchers, with the help of a professional statistical team, can try to minimize the impact of baseline data differences upon the results.

With careful research design, it is possible to consider and exclude the factors which could potentially influence the results. In doing this, and by referring to foreign research programs, this study may provide helpful information for therapeutic strategies for UIA in clinical practice. Results from this study may provide us with a chance of using normative interventions for UIA before deploying interventional treatment and craniotomy and thus provide significant benefit for patients with aneurysms.

Contributors

CD obtained the research funding and was the principal investigator of this study. YC, HF, GL, MH, YQ, XY and HZ developed the study protocol and YC was the main author of this article. HF, GL, SG and RL revised the manuscript. XS, LW, ZW, XT, MZ, MA and ZT were the main people responsible for the seven clinical centers and responsible for implementing this study. CD approved publication of the final manuscript.

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Conflict of interest
None declared

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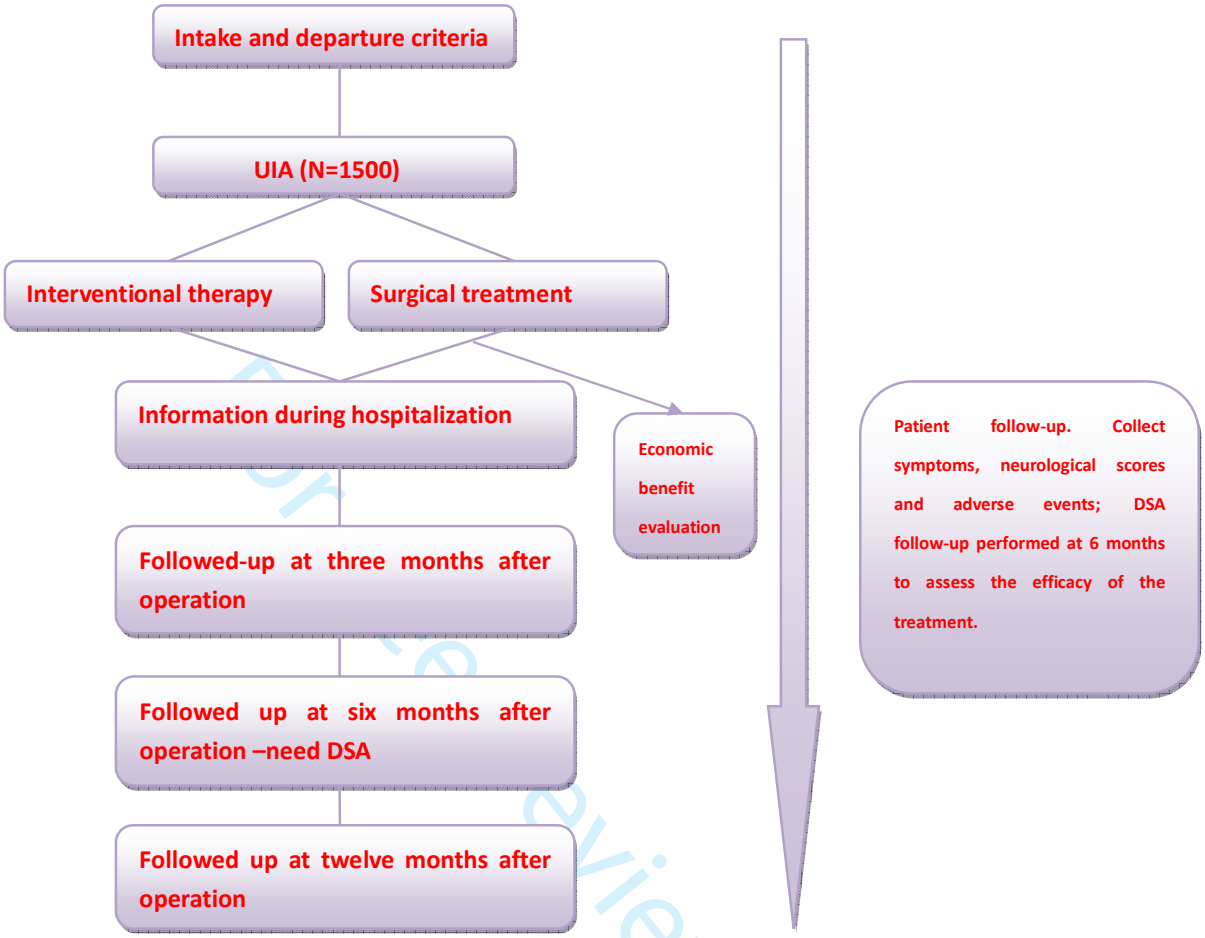
Figure 1. Research flowchart:



UIA: un-ruptured aneurysms; DSA: digital subtraction angiography

Figure 2.Subject visit and evaluation schedule.

	Screening period	Treatment period		follow-up period		
Visit number	**1**	**2**	**3**	**4**	**5**	**6**
Study	**Preoperative screening**	**In operation**	**Before discharge**	**3 months±14 days**	**6 months±30 days**	**12 months±30 days**
informed consent	√					
Intake and departure criteria	√					
Baseline information	√					
The history and history of drug	√					
Therapeutic drug	√		√	√	√	√
Symptoms and physical examination	√		√	√	√	√
electrocardiogram	√					
Routine blood test	√			√	√	√
Blood sugar	√			√	√	√
Blood lipid	√			√	√	√
Homocysteine	√					
Head CT/MRI	√		√		√	
Vascular Ultrasonography	√					
CTA/MRA/DSA	√				√	
mRS score	√		√	√	√	√
GCS score	√		√			
WFNS score	√					
MMSE score	√		√	√	√	√
Total operating cost			√			
Adverse event		√	√	√	√	√

GCS: Glasgow Coma Scale; WFNS: The World Federation of neurosurgeons; MMSE: mini-mental state examination

Table 1. Inclusion criteria.

1. At least 1 intracranial un-ruptured aneurysm confirmed by imaging (CTA/MRA/DSA), whether or not there are clinical symptoms
2. For patients with multiple aneurysms, the treatment interval is 6 months, regardless of whether they have been treated or not
3. Patients currently have the ability to live independently and have an mRS scale score of ⩽3
4. Age is > 14 years old
5. Patients or family members agree to provide informed written consent

Table 2. Exclusion criteria.

1.Intracranial aneurysms associated with unexplained subarachnoid hemorrhage for 30 days
2. Patients with other intracranial vascular malformations, such as AVM or AVF
3. Patients with intracranial or other parts of the body suffering from malignancy
4. Fusiform, traumatic, bacterial, or dissecting aneurysms
5. Patients with severe mental illness who are unable to communicate when disease is diagnosed
6. Patients with poor overall state, expected survival time less than 1 year or poor physical status, cannot tolerate general anesthesia or aneurysm surgeries
7. Patients involved in other clinical studies of intracranial aneurysms
8. Patients undergoing surgical clipping or endovascular treatment simultaneously
9. Patients who refused to follow up
10. The size of the aneurysm ⩽ 3 mm

CTA: computed tomography angiography; MRA: magnetic resonance angiography; DSA: digital subtraction angiography; AVM: arteriovenous malformation; AVF: arteriovenous fistula; mRS: modified Rankin scal

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The China intracranial aneurysm project (CIAP): protocol for a prospective cohort study of interventional treatment and craniotomy for un-ruptured aneurysms

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The China intracranial aneurysm project (CIAP): protocol for a prospective cohort study of interventional treatment and craniotomy for un-ruptured aneurysms

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ABSTRACT

Introduction: Intracranial aneurysm (IA) is a complex condition with serious side effects. There are two approaches for the treatment of IA: interventional therapy and craniotomy, both have their advantages and disadvantages in terms of treatment efficacy. To avoid the over-treatment of un-ruptured aneurysms（UIA）, save valuable medical resources, and reduce patient mortality and disability rate, it is vital that neurosurgeons select the most appropriate type of treatment to provide the best levels of care. However, making this clinical decision is difficult. Here, we propose a refined prospective, multicenter study for the Chinese population with strictly defined patient inclusion criteria, along with the selection of representative clinical participating centers.

Methods and analysis: This is a multicenter, prospective cohort study. As IA is extremely harmful if it is ruptured and ethical issues need to be taken into account, researchers are not able to use randomized controlled trials. The proposed study will be carried out by 12 clinical centers located in different regions of China. The trial recruitment programme begins in 2016 and is scheduled to be complete in 2020. We expect 1500 subjects with UIA to be included. Clinical information relating to the subjects will recorded objectively. The main endpoints are an evaluation of the safety, efficiency and economic benefits of interventional treatment and craniotomy for 6 months after surgery, with each participant completing at least one year of follow-up.

Ethics and dissemination: The research protocol and the informed consent form (ICF) for participants in this study are approved by the ethics committee of Zhujiang Hospital of Southern Medical University (2017-SJWK-001). The results of this study are expected to be disseminated in professional printed media in 2021.

Clinical Trials registration number: NTC03133598

Keywords: Un-ruptured aneurysms; Interventional treatment; Craniotomy; Prospective

Strengths and limitations of this study

1. This represents the first prospective cohort study to provide strategies for the selection of treatment options for aneurysm in China, including a number of clinical centers throughout the country, thus, it can fully represent the Chinese population.
2. Inclusion criteria and exclusion criteria are in line with foreign research programs, but have been combined with China's national conditions to formulate a reasonable research plan, which incorporates an adequate sample size to but ensures that the study can be completed on time.
3. The research process will be coordinated by several departments to ensure the quality and reliability of research data.
4. The limitation of the proposed study is that it may include multiple forms of clinical data, which may differ from the intended purpose due to human subjectivity.

INTRODUCTION

IA is a common cause of subarachnoid hemorrhage (SAH) and is estimated to affect between 0.2% and 9% of the population. While the detection rate for un-ruptured IAs (UIAs) in healthy people can be as high as 3%, these detection rates differ across different countries.[1] According to recent research, the overall prevalence of UIA is 7.0% in Chinese adults aged 35 to 75 years, with women more affected than men (8.4% *versus* 5.5%, respectively).[2] In the case of un-ruptured cerebral aneurysms (UCAS), the natural course of UIA varies according to the size, location, and shape of the aneurysm.[3] Interventional therapy and craniotomy represent the two main methods for treating UIAs. However, despite our current knowledge of UIA, and even when we take into account information relating to pathological, radiological, and clinical studies, there is still no specific criteria that can be used to select the appropriate treatment strategy. Consequently, there is an urgent global requirement to develop methods which will help in selecting the most appropriate treatment for UIA.[4]

A large number of researchers have investigated the treatment options available for IA and many of these studies indicated that the postoperative complications associated with interventional therapy are lower than those of craniotomy. However, the short and long-term occlusion rate was lower for interventional therapy than for craniotomy.[5-9] These previous studies have also highlighted that the size and anatomical location of aneurysms can exert a significant influence on the effect of treatment.[5-9] Interestingly, research failed to identify any significant difference in costs when treatment was compared between endovascular and neurosurgical approaches over the short term.[10] The International Subarachnoid Aneurysm Trial (ISAT) further showed that compared with craniotomy, interventional treatment can clearly improve patient outcome; however, most of the participants in this study had small aneurysms. Consequently, this trial could not definitively conclude that coiling is safer than clipping for all cases of IA.[11-14] While controversial, the ISAT did provide us with some degree of understanding of IA.[15 16]

Previous research has also shown that the risk of many IA rupture is 1% to 2%, and leads to intracranial hemorrhage, a dangerous condition which is associated with a high mortality and disability rate.[17] However, while UIAs do not generally rupture during long-term follow-up, some medical treatment can increase bleeding rate and the rate of rupture. Thus, in the absence of any specific guidelines for the treatment of aneurysms, the aim of this study was to assess the safety, efficacy and economic benefits of interventional treatment *versus* craniotomy, and propose a scientific strategy for selecting the appropriate form of surgical treatment for UIA, which could be deployed across clinics worldwide.

METHODS AND ANALYSIS

Study design

CIAP is an ongoing, multicenter trial supported by the National Key Research Development Program, and predominantly studies aneurysms from 5 different aspects:

1) The risk of antithrombotic therapy in patients with UIAs complicated by ischemic cardio cerebrovascular diseases; 2) The rate of rupture; 3) The risk of rupture and developing a model to predict rupture; 4) Treatment options for UIAs and 5) The development of standardized treatments for early stage UIA bleeding; this study is one of the sub-topics, is an observational study.

This study evaluates the treatment options for UIAs from the point of view of safety, efficacy and economic benefits, and compares these factors between interventional therapy and craniotomy. The incidence of aneurysms is relatively high among the population, and China is a large country with a wide population distribution. Thus, in order to fully reflect the population more objectively, the researchers using multicenter, prospective cohort study to complete this study, which will last for five continuous years continuously. Furthermore, refer to previous related research studies and take into account the characteristics and hazards of UIA，the researchers does not involve random division of subjects into groups[3] and 1500 UIA subjects are expected to be included. Each subject will be followed up at fixed time points by researchers and the normal procedures of treatment would not be affected by subjects joining the CIAP study. Follow-up data, and other clinical information, relating to the subjects are recorded in detail, and data is analyzed statistically. A concise flow chart of the entire study is shown in Figure 1. The study protocol was approved by the Ethics Committee of Zhujiang Hospital of Southern Medical University (Reference Number: 2017-SJWK-001) and its respective Institutional Review Board (IRB). The trial has been registered at ClinicalTrials.gov with reference number NTC03133598.

Participation center qualification

In order to evaluate UIA treatment objectively, it is important to avoid subject bias and ensure that an adequate number of cases are included in the study. The researchers selected 12 clinical centers (each center covering more than 2 community or referral units) to conduct this study in collaboration which distributed across several regions of China (south east, southwest, northwest, northeast). According to an incomplete dataset; in 2015, a total of 6000 IA patients had been evaluated across the 12 clinical centers. Consequently, the researchers believe that each center can adequately represent the real level of IA diagnosis and treatment at a regional and national level. The12 clinical centers are therefore representative.

There are no specific guidelines for the treatment of UIA. As such, differences exist in the diagnosis and treatment of IA across different regions, different centers, and even between different neurosurgeons. in this study, the basic requirement of neurosurgeons who performs surgery on subjects is able to complete the aneurysm surgery more than 30 cases per year independently. The study also features an imaging interpretation center (Internationally Recognized Image Interpretation Laboratory, established by Xuanwu Hospital and Image Center of the University of California, Los Angeles, UCLA); this center is responsible for the unified standard interpretation of imaging data arising from the 12 clinical centers.

Subjects selection and screening

The purpose of this study is to recruit patients who are suffering IA without rupture. First, subjects are diagnosed with UIA, either by computed tomography angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA). Patients with fusiform, traumatic, bacterial or dissecting aneurysms, or with SAH of unknown origin, are excluded. These types of patients, involving other vascular diseases (arteriovenous malformation [AVM], arteriovenous fistula [AVF]), malignant tumors, or poor physical condition factors are expected to live for less than a year, therefore, all not suitable for study. In order not to disturb the objectivity of the study and provide good opportunities for follow-up, the researchers also emphasized the ability of subjects to live independently (using the modified Rankin scale (mRS) and included those with a score of $\leqslant$3). Patients were also excluded if they were unable to communicate normally due to serious mental illness; the size of the aneurysm was less than 3 mm; the diagnosis of aneurysms is unclear or difficult. The specific inclusion and exclusion criteria for the trial are provided in Table 1 and Table 2, respectively.

The study involves twelve recruiting centers, each of which requiring IRB approval before recruiting cases. Patients diagnosed with UIA not only receive formal diagnosis and treatment for their aneurysms, but also, along with their families, receive full communication from the researchers, with regard to the aims of the study. Patients can then voluntarily join the study and sign the ICF. Once this is done, the subject's imaging data will be transmitted to the imaging interpretation center to re-confirm the diagnosis. If the two diagnoses are not consistent, then the subject is excluded. The subjects can withdraw from the study at any time, and the researchers can determine whether the subjects continue the study according to their physical status. When serious adverse events occur during the course of the trial, the researchers must terminate the study in advance and report to the ethics committee; adverse events are also entered into the case report form (CRF). This study is an observational study that does not interfere with the normal course of clinical diagnosis and treatment; even if subjects withdraw from the study, it would not affect their treatment.

Sample size calculation

Calculating sample size based on formula:

$$n = \frac{(z_\alpha \sqrt{(1 + 1/R)\bar{p}\bar{q}} + z_\beta \sqrt{p_1 q_1 + p_0 q_0 / R})^2}{(P_1 - P_0)^2}$$

($\alpha = 0.05$, two-sided test, 80% of the degree of control.)

According to the results of ISUA test, the mortality rate of the intervention group was

8.7% in one year and that of the craniotomy group was 14.1%, and the intervention group was two times as much as subjects as those in the craniotomy group, we calculated that n=1185 (intervention group: n = 395; craniotomy group: n = 790). During the study, 20% of the patients would be missed follow-up, so, the study requires 1,400 subjects. The study finally decided to include 1,500 subjects.

Data collection

Once subjects are included in the study, all information about the course of diagnosis and treatment are recorded in the CRF. This study also uses an electronic data collection system (EDC) developed by the National Center for Cardiovascular Disease; information stored on CRFs are entered into the EDC by a designated person on each site, and each site shares data with the EDC. The objective of this study was to objectively compare the safety, efficacy and economic benefits of the two treatment methods for UIA, and each subject followed for at least one year (at 3, 6, and 12 months), follow-up data were acquired by a neurosurgeon either by telephone or by social tools as soon as possible. In most cases, DSA examination should be carried out six months after the operation to confirm the effect of treatment, which is the vital end point of this study. Besides, data acquired at three and twelve months after surgery are also an important aspect of the study. A detailed follow-up plan is given in Figure 2. During the study, the researchers were obliged to protect the personal privacy and medical information of each subject, and strictly adhere to ethical guidelines.

Data management

As all data will be collected using CRFs and the EDC, the CIAP have established a data management committee (DMC, located in Xuanwu hospital) to supervise data quality, and hired a special data management company responsible for constructing the EDC and ensuring data security, integrity and accuracy. Before the subjects are formally enrolled, the DMC holding CRF and EDC data entry study classes for main researches in each collaboration clinical center; considers data entry, modification and retrieval, and sets permissions for the main researchers in the EDC. A clinical research operator (CRO) supervises project progress and quality of data implementation, and the researcher assigned, the clinical research associate (CRA) regularly visits each participating center to ensure that all contents of the research program are strictly adhered to; if not, the CRA promptly submits information to the investigators. Throughout the project, a research summary conference will be held every 6 months, to discuss progress and solve any problems that may arise.

Data analysis

The Department of Medical Statistics at the National Center for Cardiovascular Diseases is responsible for all data management and statistical analysis. SPSS V21.0 statistical software (IBM Corp, Armonk, New York, USA) is used to analyze the results, with normally distributed data represented by $\bar{x}$ ±SD. Skewed distribution data is described by the median (*M*) and the four quartile range (*P25; P75*), using an independent t test or rank sum test. Categorical variables are described by frequency

and percentage and grouped data, rate or percentages between the groups are compared with the Chi square test or Fisher exact test. Rank data is analyzed by the rank sum test. $P<0.05$ was considered to indicate statistical significance.

Endpoints of the study

The endpoints of the study were also divided into primary and secondary endpoints. The safety and effectiveness of interventional and craniotomy are considered as the primary endpoint of the study, and they are the goals of investigator. Using the subjects' mortality and morbidity rate to evaluated the safety of interventional and craniotomy, in addition, ipsilateral stroke and neurological deficits within 30 days Ipsilateral stroke and neurological deficits within 30 days supplemented the safety evaluation of our study and will play a positive role in our findings. The effectiveness is evaluated with aneurysm recurrence rate, re-bleeding rate and complete occlusion rate. The secondary end point mainly considered the time of postoperative evaluation and the occurrence of adverse events. The primary endpoint and the secondary endpoint are detailed in Table 3.

DISCUSSION

To our best knowledge, CIAP is the project to explore the characteristics of Chinese intracranial aneurysms within the nation of Chinese people, and does so from a range of different aspects: the rate of spontaneous aneurysm rupture; risk factors of rupture; and the emergency treatment required for ruptured aneurysms; etc., in particular, the study compares two different treatment methods for UIA. IA is a common cause of SAH, but this does not mean that the SAH rate is high so that the incidence of IA is also high,[18] SAH can lead to an erroneous understanding of IA to a certain extent. Consequently, we should exclude the unknown causes of SAH.[19] DSA has traditionally been considered the gold standard for detecting aneurysms. However, combined with existing data, indicates that the incidence of UIA within the population varies according to the method of examination, the main reason for this is that the accuracy of different diagnostic methods is affected by the size of aneurysms. Studies have shown that the sensitivity of DSA is only 85% for small aneurysms (<3 mm), and that the efficacy of computed tomographic (CT) angiography for diagnosing intracranial aneurysms is increasingly being recognized,[1 20-23] this study excludes patients with small aneurysms, and in doing so, increases the accuracy of the study. This, however, means that the study can be considered as incomplete as it only targets in aneurysms of a certain size.

The treatment of IA cannot be separated from interventional treatment and craniotomy. Interventional therapy is becoming more and more popular among neurosurgeons, but selecting which of the two approaches to use for treatment has been controversial.[24-26] Most scholars believe that interventional therapy is associated with lower mortality compared with craniotomy, which the recurrence and re-bleeding rate of interventional therapy is higher,[12] and combined with other techniques may achieve better results.[5 27 28] The recurrence rate of interventional therapy is higher because for

certain types of aneurysms, such as wide neck aneurysms, the treatment effect is not satisfactory. However, as the intervention materials and technology improves, many scholars have adopted this approach for the treatment of aneurysms and have obtained good results. [29-33] Comparing the two methods in terms of safety and effectiveness, it is necessary to consider a range of factors, such as age, gender, subarachnoid hemorrhage and aneurysm size; because these are the principal factors which can influence the re-bleeding of aneurysms.[34 35] Surgery can cause hemodynamic changes of an aneurysm, but there is no conclusive evidence to show that this plays a positive role in the recurrence of aneurysms, the study does not take into account the effects of hemodynamics on the results,[36 37] rather, the researchers, with the help of a professional statistical team, can try to minimize the impact of baseline data differences upon the results.

With careful research design, it is possible to consider and exclude the factors which could potentially influence the results, and by referring to foreign research programs, this study may provide helpful information for therapeutic strategies for UIA in clinical practice. Results from this study may provide us with a chance of using normative interventions for UIA before deploying interventional treatment and craniotomy and thus provide significant benefit for patients with aneurysms.

Contributors

CD obtained the research funding and was the principal investigator of this study. YC, HF, XL, MH, YQ, XY and HZ developed the study protocol and YC was the main author of this article. HF, XH, SG and XL revised the manuscript. XS, LW, ZW, XT, MZ, MA and ZT were the main people responsible for the seven clinical centers and responsible for implementing this study. CD approved publication of the final manuscript.

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Conflict of interest

None declared

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Table 1. Inclusion criteria.

1. At least 1 intracranial un-ruptured aneurysm confirmed by imaging (CTA/MRA/DSA), whether or not there are clinical symptoms
2. For patients with multiple aneurysms, the treatment interval is 6 months, regardless of whether they have been treated or not
3. Patients currently have the ability to live independently and have an mRS scale score of ⩽3
4. Age is > 14 years old
5. Patients or family members agree to provide informed written consent

Table 2. Exclusion criteria.

1.Intracranial aneurysms associated with unexplained subarachnoid hemorrhage for 30 days
2. Patients with other intracranial vascular malformations, such as AVM or AVF
3. Patients with intracranial or other parts of the body suffering from malignancy
4. Fusiform, traumatic, bacterial, or dissecting aneurysms
5. Patients with severe mental illness who are unable to communicate when disease is diagnosed
6. Patients with poor overall state, expected survival time less than 1 year or poor physical status, cannot tolerate general anesthesia or aneurysm surgeries
7. Patients involved in other clinical studies of intracranial aneurysms
8. Patients undergoing surgical clipping or endovascular treatment simultaneously
9. Patients who refused to follow up
10. The size of the aneurysm ⩽ 3 mm

CTA: computed tomography angiography; MRA: magnetic resonance angiography; DSA: digital subtraction angiography; AVM: arteriovenous malformation; AVF: arteriovenous fistula; mRS: modified Rankin scale

Table3. endpoints of the study

1.The primary endpoint

①The main security endpoint:

The safety evaluation of interventional therapy and craniotomy clipping when the subjects are treated for 6 months: including subjects' mortality (mRS = 6), morbidity (3 ⩽ mRS ⩽ 5 points); the emergency of ipsilateral stroke and neurological deficits within 30 days are also recognized as reliability measures to evaluate the security of interventional and craniotomy.

②The main effectiveness endpoint:

The effectiveness evaluation of interventional therapy and craniotomy clipping when the subjects are treated for 6 months: including the recurrence(Raymond classification=1) rate and complete occlusion (Raymond classification=1) rate of aneurysms, re-bleeding rate of subjects.

2. The secondary endpoints

① The safety evaluation of interventional therapy and craniotomy clipping when the subjects are treated for 12 months: including subjects' mortality (mRS = 6), morbidity (3 ⩽ mRS ⩽ 5 points);

② The effectiveness evaluation of interventional therapy and craniotomy clipping when the subjects are treated for 12 months: including the recurrence(Raymond classification=1) rate and complete occlusion (Raymond classification=1) rate of aneurysms, re-bleeding rate of subjects;

③The success rate of treatment;

④The success rate of 6 months after interventional therapy or craniotomy clipping(the DSA hint: aneurysm completely or nearly total occlusion, re-canalization or re-growth did not appear);

⑤The incidence of major adverse events during hospitalization;

⑥The incidence of major adverse events after 3months of surgery;

⑦The incidence of major adverse events in 3months and 6months later after operation;

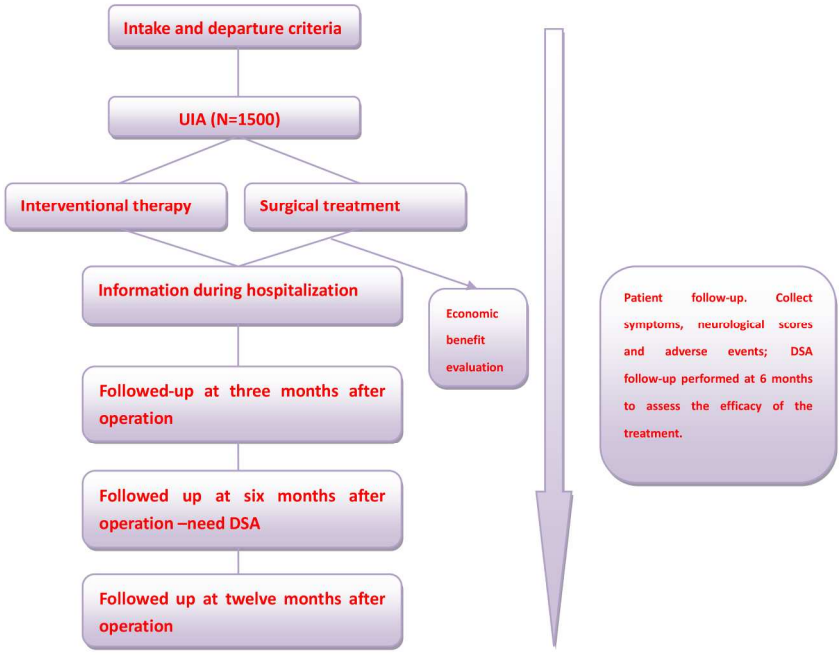
⑧The incidence of major adverse events in 6months and 12months later after operation.

Figure legends

Figure1.Research flowchart

Figure2.Subject visit and evaluation schedule

Figure 1. Research flowchart:



UIA: un-ruptured aneurysms; DSA: digital subtraction angiography

169x243mm (300 x 300 DPI)

Figure 2.Subject visit and evaluation schedule.

	Screening period	Treatment period		follow-up period		
Visit number	**1**	**2**	**3**	**4**	**5**	**6**
Study	**Preoperative screening**	**In operation**	**Before discharge**	**3 months±14 days**	**6 months±30 days**	**12 months±30 days**
informed consent	√					
Intake and departure criteria	√					
Baseline information	√					
The history and history of drug	√					
Therapeutic drug	√		√	√	√	√
Symptoms and physical examination	√		√	√	√	√
electrocardiogram	√					
Routine blood test	√			√	√	√
Blood sugar	√			√	√	√
Blood lipid	√			√	√	√
Homocysteine	√					
Head CT/MRI	√		√		√	
Vascular Ultrasonography	√					
CTA/MRA/DSA	√				√	
mRS score	√		√	√	√	√
GCS score	√		√			
WFNS score	√					
MMSE score	√		√	√	√	√
Total operating cost			√			
Adverse event		√	√	√	√	√

GCS: Glasgow Coma Scale; WFNS: The World Federation of neurosurgeons; MMSE: mini-mental state examination

154x231mm (300 x 300 DPI)

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The China intracranial aneurysm project (CIAP): protocol for a prospective cohort study of interventional treatment and craniotomy for un-ruptured aneurysms

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Keywords:	Un-ruptured aneurysms, Interventional treatment, Craniotomy, Prospective

The China intracranial aneurysm project (CIAP): protocol for a prospective cohort study of interventional treatment and craniotomy for un-ruptured aneurysms

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ABSTRACT

Introduction: Intracranial aneurysm (IA) is a complex condition with serious side effects. There are two approaches for the treatment of IA: interventional therapy and craniotomy, both of these approaches have their advantages and disadvantages in terms of treatment efficacy. To avoid the over-treatment of un-ruptured aneurysms （UIA）, save valuable medical resources, and reduce patient mortality and disability rate, it is vital that neurosurgeons select the most appropriate type of treatment to provide the best levels of care. However, making this clinical decision is difficult. Here, we propose a refined prospective, multicenter study for the Chinese population with strictly defined patient inclusion criteria, along with the selection of representative clinical participating centers.

Methods and analysis: This is a multicenter, prospective cohort study. As IA is extremely harmful if it is ruptured. Therefore, ethical issues need to be taken into account with regard to this study and researchers are not, therefore, able to use randomized controlled trials. The proposed study will be carried out by 12 clinical centers located in different regions of China. The trial recruitment programme begins in 2016 and is scheduled to be completed in 2020. We expect 1500 participants with UIA to be included. Clinical information relating to the participants will be recorded objectively. The main endpoints are an evaluation of the safety, efficiency and economic benefits of interventional treatment and craniotomy for 6 months after surgery, with each participant completing at least one year of follow-up.

Primary and secondary endpoints: The primary endpoint of this study is safety and efficacy when participants are treated for 6 months. The second endpoint is the evaluation of safety and the efficacy of interventional therapy and craniotomy clipping when participants are treated for 12 months. We also address the success of treatment and the incidence of adverse events.

Ethics and dissemination: The research protocol and the informed consent form (ICF) for participants in this study are approved by the ethics committee of Zhujiang Hospital of Southern Medical University (2017-SJWK-001). The results of this study are expected to be disseminated in the professional printed media in 2021.

Clinical Trials registration number: NTC03133598

Keywords: Un-ruptured aneurysms; Interventional treatment; Craniotomy; Prospective

Strengths and limitations of this study

1. This represents the first prospective cohort study to provide strategies for the selection of treatment options for aneurysm in China, including a number of clinical centers throughout the country, thus, it can fully represent the Chinese population.
2. Inclusion criteria and exclusion criteria are in line with foreign research programs, but have been adopted in the light of China's national conditions to formulate a reasonable research plan, which incorporates an adequate sample size to but ensures that the study can be completed on time.

3. The research process will be coordinated by several departments to ensure the quality and reliability of the research data.
4. The proposed study features some limitations which need to be considered. For example, it includes multiple clinical data and multiple control clinical factors, and the treatment process involves human subjectivity. These factors may bias the conclusions arising from this study.

INTRODUCTION

IA is a common cause of subarachnoid hemorrhage (SAH) and is estimated to affect between 0.2% and 9% of the population. While the detection rate for un-ruptured IAs (UIAs) in healthy people can be as high as 3%, these detection rates differ across different countries.[1] According to recent research, the overall prevalence of UIA is 7.0% in Chinese adults aged 35 to 75 years, with women more affected than men (8.4% *versus* 5.5%, respectively).[2] In the case of un-ruptured cerebral aneurysms (UCAS), the natural course of UIA varies according to the size, location, and shape of the aneurysm.[3] Interventional therapy and craniotomy represent the two main methods for treating UIAs. However, despite our current knowledge of UIA, and even when we take into account information relating to pathological, radiological, and clinical studies, there are still no specific criteria that can be used to select the appropriate treatment strategy. Consequently, there is an urgent global requirement to develop methods which will help in selecting the most appropriate treatment for UIA.[4]

A large number of researchers have investigated the treatment options available for IA and many of these studies have indicated that the postoperative complications associated with interventional therapy are lower than those of craniotomy. However, the short and long-term occlusion rate was lower for interventional therapy than for craniotomy.[5-9] These previous studies have also highlighted that the size and anatomical location of aneurysms can exert a significant influence on the effect of treatment.[5-9] Interestingly, research failed to identify any significant difference in costs when treatment was compared between endovascular and neurosurgical approaches over the short term.[10] The International Subarachnoid Aneurysm Trial (ISAT) further showed that compared with craniotomy, interventional treatment can clearly improve patient outcome; however, most of the participants in this study had small aneurysms. Consequently, this trial could not definitively conclude that coiling is safer than clipping for all cases of IA.[11-14] While controversial, the ISAT did provide us with some degree of understanding of IA.[15 16]

Previous research has also shown that the risk of many IA rupture is 1% to 2%, and leads to intracranial hemorrhage, a dangerous condition which is associated with a high mortality and disability rate.[17] However, while UIAs do not generally rupture during long-term follow-up, some medical treatment can increase bleeding rate and the rate of rupture. Thus, in the absence of any specific guidelines for the treatment of aneurysms, the aim of this study was to assess the safety, efficacy and economic benefits of interventional treatment *versus* craniotomy, and to propose a scientific

strategy for selecting the appropriate form of surgical treatment for UIA, which could be deployed across clinics worldwide.

METHODS AND ANALYSIS

Study design

CIAP is an ongoing, multicenter trial supported by the National Key Research Development Program, and predominantly studies aneurysms from five different aspects: 1) The risk of antithrombotic therapy in patients with UIAs complicated by ischemic cardio cerebrovascular diseases; 2) The rate of rupture; 3) The risk of rupture and developing a model to predict rupture; 4) Treatment options for UIAs and 5) The development of standardized treatments for early stage UIA bleeding; this study is one of the sub-topics, is an observational study.

This study evaluates the treatment options for UIAs from the point of view of safety, efficacy and economic benefits, and compares these factors between interventional therapy and craniotomy. The incidence of aneurysms is relatively high among the population, and China is a large country with a wide population distribution. Thus, in order to fully reflect the population more objectively, the researchers will carry out this multicenter, prospective cohort study, which will last for five continuous years. Furthermore, referring to previous related research studies and taking into account the characteristics and hazards of UIA，the researchers will not include the random division of participants into groups[3] and 1500 UIA participants are expected to be included. Each participant will be followed up at fixed time points by researchers and the normal procedures of treatment will not be affected by participants joining the CIAP study. Follow-up data, and other clinical information, relating to the participants are recorded in detail, and data is analyzed statistically. A concise flow chart of the entire study is shown in Figure 1. The study protocol was approved by the Ethics Committee of Zhujiang Hospital of Southern Medical University (Reference Number: 2017-SJWK-001) and its respective Institutional Review Board (IRB). The trial has been registered at ClinicalTrials.gov with reference number NTC03133598.

Participation center qualification

In order to evaluate UIA treatment objectively, it is important to avoid participant bias and to ensure that an adequate number of cases are included in the study. The researchers selected 12 clinical centers (each center covering more than 2 community or referral units) to conduct this study in collaboration which distributed across several regions of China (south east, southwest, northwest and northeast). According to an incomplete dataset, in 2015 a total of 6000 IA patients had been evaluated across the 12 clinical centers. Consequently, the researchers believe that each center can adequately represent the real level of IA diagnosis and treatment at a regional and national level. The12 clinical centers used in this study are therefore representative.

There are no specific guidelines for the treatment of UIA. As such, differences exist in the diagnosis and treatment of IA across different regions, different centers, and even

between different neurosurgeons. In this study, the basic requirement of the neurosurgeons who perform surgery on participants is that they are able to complete the aneurysm surgery in more than 30 cases per year independently. The study also features an imaging interpretation center (Internationally Recognized Image Interpretation Laboratory, established by Xuanwu Hospital and the Image Center of the University of California, Los Angeles, UCLA); this center is responsible for the unified standard interpretation of imaging data arising from the 12 clinical centers.

Participant **selection and screening**

The purpose of this study is to recruit patients who are suffering IA without rupture. First, participants are diagnosed with UIA, either by computed tomography angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA). Patients with fusiform, traumatic, bacterial or dissecting aneurysms, or with SAH of unknown origin, are excluded. These types of patients, involving other vascular diseases (arteriovenous malformation [AVM], arteriovenous fistula [AVF]), malignant tumors, or poor physical condition factors are expected to live for less than a year, and are not suitable for study. In order not to disturb the objectivity of the study and provide good opportunities for follow-up, the researchers also emphasize the ability of participants to live independently (using the modified Rankin scale (mRS) and included those with a score of $\leqslant$3). Patients are also excluded if they are unable to communicate normally due to serious mental illness; if they receive flow diversion as part of their aneurysm treatment(as flow diversion becomes a standard of care for many large, wide-necked aneurysms, which are located in the internal carotid artery); if the size of the aneurysm was less than 3 mm; or if aneurysm diagnosis is unclear or difficult. The specific inclusion and exclusion criteria for the trial are provided in Tables 1 and 2, respectively.

The study involves twelve recruiting centers, each of which require IRB approval before recruiting cases. Patients diagnosed with UIA not only receive formal diagnosis and treatment for their aneurysms, but also, along with their families, receive full communication from the researchers, with regard to the aims of the study. Patients can then voluntarily join the study and sign the ICF. Once this is done, the participant's imaging data will be transmitted to the imaging interpretation center to re-confirm the diagnosis. If the two diagnoses are not consistent, then the participant is excluded. The participants can withdraw from the study at any time, and the researchers can determine whether the participants continue the study according to their physical status. When serious adverse events occur during the course of the trial, the researchers must terminate the study in advance and report to the ethics committee; adverse events are also entered into the case report form (CRF). This study is an observational study that does not interfere with the normal course of clinical diagnosis and treatment; even if participants withdraw from the study, it will not affect their treatment.

Sample size calculation

Calculating sample size based on the formula:

$$n = \frac{(z_\alpha \sqrt{(1 + 1/R)\bar{p}\bar{q}} + z_\beta \sqrt{p_1 q_1 + p_0 q_0 / R})^2}{(P_1 - P_0)^2}$$

(α = 0.05, two-sided test, 80% of the degree of control.)

According to the results of ISUA test, the mortality rate of the intervention group was 8.7% in one year and that of the craniotomy group was 14.1%, and the intervention group was two times as much as in the participants as those in the craniotomy group, we calculated that n=1185 (intervention group: n = 395; craniotomy group: n = 790). During the study, 20% of the patients would be lost during follow-up, thus, the study requires 1,422 participants. Ultimately, we decided to include 1,500 participants.

Data collection

Once participants are included in the study, all information about the course of diagnosis and treatment are recorded in the CRF-A. This study also uses an electronic data collection system (EDC) developed by the National Center for Cardiovascular Disease; information stored on CRFs is entered into the EDC by a designated person on each site, and each site shares data with the EDC. The objective of this study is to objectively compare the safety, efficacy and economic benefits of the two treatment methods for UIA, and each participant is followed for at least one year (at 3, 6, and 12 months). Consequently, each participant will have at least one year of follow-up data, and when the study is finished, participants will be followed at least once a year until 5 years. All participants undergo DSA at 18 months. Follow-up data will be acquired by a neurosurgeon either by telephone or by social tools as soon as possible and recorded in the CRF-B. In most cases, DSA examination should be carried out six months after the operation to confirm the effect of treatment, which is the vital end point of this study. Furthermore, data acquired at three and twelve months after surgery are also an important aspect of the study. A detailed follow-up plan is given in Figure 2. During the study, the researchers will be obliged to protect the personal privacy and medical information of each participant, and strictly adhere to ethical guidelines.

Data management

As all data will be collected using CRFs and the EDC, the CIAP have established a data management committee (DMC, located in Xuanwu hospital) to supervise data quality, and have hired a specialist data management company responsible for constructing the EDC and ensuring data security, integrity and accuracy. Before the participants are formally enrolled, the DMC holding CRF and EDC data entry study classes for the main researches in each collaboration clinical center; considers data entry, modification and retrieval, and sets permissions for the main researchers in the EDC. A clinical research operator (CRO) supervises project progress and quality of

data implementation, and the researcher assigned, the clinical research associate (CRA) will regularly visit each participating center to ensure that all contents of the research program are strictly adhered to; if not, the CRA promptly submits information to the investigators. Throughout the project, a research summary conference will be held every 6 months, to discuss progress and solve any problems that may arise.

Data analysis

The Department of Medical Statistics at the National Center for Cardiovascular Diseases will be responsible for all data management and statistical analysis. SPSS V21.0 statistical software (IBM Corp, Armonk, New York, USA) will be used to analyze the results, with normally distributed data represented by $\bar{x}$ ±SD. Skewed distribution data will be described by the median (*M*) and the four quartile range (*P25; P75*), using an independent t test or rank sum test. Categorical variables will be described by frequency, percentage and grouped data, and rate or percentages between the groups will be compared with the Chi square test or by the Fisher exact test. Rank data will be analyzed by the rank sum test. $P<0.05$ will be considered to indicate statistical significance.

Endpoints of the study

The endpoints of the study have also been divided into primary and secondary endpoints. The safety and efficacy of interventional treatment and craniotomy are considered as the primary endpoint of the study, and represent the key goals of investigators. Using the participant mortality and morbidity rates to evaluated the safety of interventional and craniotomy, and by considering ipsilateral stroke and neurological deficits within 30 days, we shall enhance the safety evaluation of our study and these features will play a positive role in our findings. Efficacy will be evaluated by aneurysm recurrence rate, re-bleeding rate and complete occlusion rate. The secondary endpoint mainly considers the time of postoperative evaluation and the occurrence of adverse events. The primary endpoint and the secondary endpoint are described in Table 3.

Methods of evaluating the economic benefits of treatment

The study combines the following three aspects of patient evaluation in terms of the economic benefits of treatment: admission(GCS, WFNS, mRS, MMSE), the third day after surgery (GCS, WFNS, mRS, MMSE) and the total cost of hospitalization. Multivariate logistic regression analyses will be used to adjust for GCS, WFNS, mRS, MMSE(admission and the third day after surgery),and then to compare the total cost of hospitalization for both treatments with control of other economic factors, such as length of ICU stay, length of hospital stay, readmission rate, drug changes, adverse events, intraoperation complications and postoperative complications, etc..

DISCUSSION

To the best of our knowledge, CIAP is the project to explore the characteristics of

Chinese intracranial aneurysms within the nation of Chinese people, and does so from a range of different aspects: the rate of spontaneous aneurysm rupture; risk factors of rupture; and the emergency treatment required for ruptured aneurysms; etc., in particular, this study compares two different treatment methods for UIA. IA is a common cause of SAH, but this does not imply that the SAH rate is high the incidence of IA therefore also high,[18] to a certain extent, SAH can lead to an erroneous understanding of IA. Consequently, we should exclude the unknown causes of SAH.[19] DSA has traditionally been considered the gold standard for detecting aneurysms. However, combined with existing data, the present study indicates that the incidence of UIA within the population varies according to the method of examination; the main reason for this is that the accuracy of different diagnostic methods is affected by the size of aneurysms. Studies have shown that the sensitivity of DSA is only 85% for small aneurysms (<3 mm), and that the efficacy of computed tomographic (CT) angiography for diagnosing intracranial aneurysms is increasingly being recognized;[1] [20-23] this study excludes patients with small aneurysms and, in doing so, increases the accuracy of the study. This, however, means that the study can be considered as incomplete, as it only targets in aneurysms of a certain size.

The treatment of IA cannot be separated from interventional treatment and craniotomy. Interventional therapy is becoming more and more popular among neurosurgeons, but selecting which of the two approaches to use for treatment has been controversial.[24-26] Most scholars believe that interventional therapy is associated with lower mortality compared with craniotomy, in which the recurrence and re-bleeding rate of interventional therapy is higher,[12] and combined with other techniques it may achieve better results.[5 27 28] The recurrence rate of interventional therapy is higher because for certain types of aneurysms, such as wide neck aneurysms, the treatment effect is not satisfactory. However, as the intervention materials and technology improve, many scholars have adopted this approach for the treatment of aneurysms and have obtained good results. [29-33] Comparing the two methods in terms of safety and efficacy, it is necessary to consider a range of factors, such as age, gender, subarachnoid hemorrhage and aneurysm size; because these are the principal factors which can influence the re-bleeding of aneurysms.[34 35] Surgery can cause hemodynamic changes in an aneurysm, but there is no conclusive evidence to show that this plays a positive role in the recurrence of aneurysms, the study does not take into account the effects of hemodynamics on the results,[36 37]but rather, the researchers, with the help of a professional statistical team, can try to minimize the impact of baseline data differences upon the results.

The authors believe that the most obvious limitations of this study lie in the following points. First of all, this study is a multicenter study involving 12 clinical centers that fully demonstrate the diagnosis and treatment of IA. However, each clinical center may not necessarily have the same view of treatment for IA, and there may be differences in the sources of the original data, but multicenter research is essential for this study. Secondly, in the study process, there are many factors affecting outcome, including treatment time, drug changes and adverse events, etc.. These are very

difficult to avoid in clinical studies, so the control of clinical factors is fine in our study design. In addition, our study includes 1,500 participants. Whether this sample accurately represents the Chinese patients with IA is unknown; there are no national studies to indicate the overall incidence of IA in China, and we can only refer to the existing literature. CIAP sub-project 1aims to indicate the incidence of IA in China.

With careful research design, it is possible to consider and exclude the factors that could potentially influence the results, and by referring to foreign research programs, this study may provide helpful information for therapeutic strategies for UIA in clinical practice. Results from this study may provide us with a chance of using normative interventions for UIA before deploying interventional treatment and craniotomy and thus provide significant benefit for patients with aneurysms.

Contributors

CD obtained the research funding and is the principal investigator of this study. YC, HF, XL, MH, YQ, XY and HZ have developed the study protocol and YC is the main author of this article. HF, XH, SG and XL have revised the manuscript. XS, LW, ZW, XT, MZ, MA and ZT are the main people responsible for the seven clinical centers and responsible for implementing this study. CD has approved publication of the final manuscript.

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Conflict of interest

None declared

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Table 1. Inclusion criteria.

1. At least 1 intracranial un-ruptured aneurysm confirmed by imaging (CTA/MRA/DSA), whether or not there are clinical symptoms
2. For patients with multiple aneurysms, the treatment interval is 6 months, regardless of whether they have been treated or not
3. Patients currently have the ability to live independently and have an mRS scale score of ⩽3
4. Age is > 14 years old
5. Patients or family members agree to provide informed written consent

Table 2. Exclusion criteria.

1.Intracranial aneurysms associated with unexplained subarachnoid hemorrhage for 30 days
2. Patients with other intracranial vascular malformations, such as AVM or AVF
3. Patients with intracranial or other parts of the body suffering from malignancy
4. Fusiform, traumatic, bacterial, or dissecting aneurysms
5. Patients with severe mental illness who are unable to communicate when disease is diagnosed
6. Patients with poor overall state, expected survival time less than 1 year or poor physical status, cannot tolerate general anesthesia or aneurysm surgeries
7. Patients involved in other clinical studies of intracranial aneurysms
8. Patients undergoing surgical clipping or endovascular treatment simultaneously
9. Patients who receive flow diversion as aneurysm treatment
10. Patients who refused to follow up
11. The size of the aneurysm ⩽ 3 mm

CTA: computed tomography angiography; MRA: magnetic resonance angiography; DSA: digital subtraction angiography; AVM: arteriovenous malformation; AVF: arteriovenous fistula; mRS: modified Rankin scale

Table3. endpoints of the study

1.The primary endpoint

①The main security endpoint:

The safety evaluation of interventional therapy and craniotomy clipping when the participants are treated for 6 months: including participants' mortality (mRS = 6), morbidity (3 ⩽ mRS ⩽ 5 points); the emergency of ipsilateral stroke and neurological deficits within 30 days are also recognized as reliability measures to evaluate the security of interventional and craniotomy.

②The main effectiveness endpoint:

The effectiveness evaluation of interventional therapy and craniotomy clipping when the participants are treated for 6 months: including the recurrence(Raymond classification=1) rate and complete occlusion (Raymond classification=1) rate of aneurysms, re-bleeding rate of subjects.

2. The secondary endpoints

① The safety evaluation of interventional therapy and craniotomy clipping when the participants are treated for 12 months: including participants ' mortality (mRS = 6), morbidity (3 ⩽ mRS ⩽ 5 points);

② The effectiveness evaluation of interventional therapy and craniotomy clipping when the participants are treated for 12 months: including the recurrence(Raymond classification=1) rate and complete occlusion (Raymond classification=1) rate of aneurysms, re-bleeding rate of subjects;

③The success rate of treatment;

④The success rate of 6 months after interventional therapy or craniotomy clipping(the DSA hint: aneurysm completely or nearly total occlusion, re-canalization or re-growth did not appear);

⑤The incidence of major adverse events during hospitalization;

⑥The incidence of major adverse events after 3months of surgery;

⑦The incidence of major adverse events in 3months and 6months later after operation;

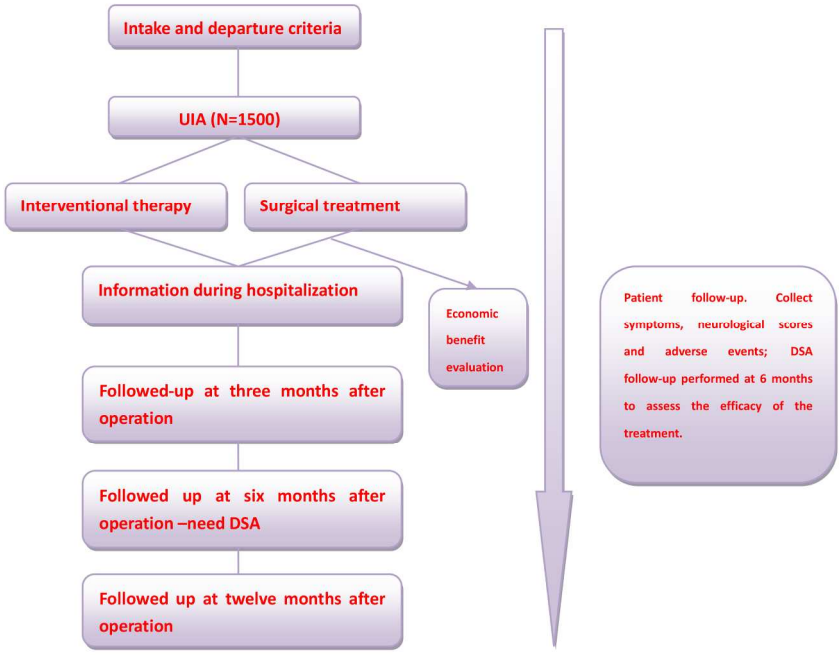
⑧The incidence of major adverse events in 6months and 12months later after operation.

Figure legends

Figure1.Research flowchart

Figure2. Participants visit and evaluation schedule

Figure 1. Research flowchart:



UIA: un-ruptured aneurysms; DSA: digital subtraction angiography

169x243mm (300 x 300 DPI)

Figure 2. Participants **visit and evaluation schedule.**

	Screening period	Treatment period		follow-up period		
Visit number	**1**	**2**	**3**	**4**	**5**	**6**
Study	**Preoperative screening**	**In operation**	**Before discharge**	**3 months±14 days**	**6 months±30 days**	**12 months±30 days**
informed consent	√					
Intake and departure criteria	√					
Baseline information	√					
The history and history of drug	√					
Therapeutic drug	√		√	√	√	√
Symptoms and physical examination	√		√	√	√	√
electrocardiogram	√					
Routine blood test	√			√	√	√
Blood sugar	√			√	√	√
Blood lipid	√			√	√	√
Homocysteine	√					
Head CT/MRI	√		√		√	
Vascular Ultrasonography	√					
CTA/MRA/DSA	√				√	
mRS score	√		√	√	√	√
GCS score	√		√			
WFNS score	√					
MMSE score	√		√	√	√	√
Total operating cost			√			
Adverse event		√	√	√	√	√

GCS: Glasgow Coma Scale; WFNS: The World Federation of neurosurgeons; MMSE: mini-mental state examination

210x297mm (300 x 300 DPI)

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The China intracranial aneurysm project (CIAP): protocol for a prospective cohort study of interventional treatment and craniotomy for un-ruptured aneurysms

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Keywords:	Un-ruptured aneurysms, Interventional treatment, Craniotomy, Prospective

The China intracranial aneurysm project (CIAP): protocol for a prospective cohort study of interventional treatment and craniotomy for un-ruptured aneurysms

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ABSTRACT

Introduction: There are two approaches for the treatment of IA: interventional therapy and craniotomy, both of which have their advantages and disadvantages in terms of treatment efficacy. To avoid the over-treatment of un-ruptured aneurysms （UIA）, to save valuable medical resources, and to reduce patient mortality and disability rate, it is vital that neurosurgeons select the most appropriate type of treatment to provide the best levels of care. In this study, we propose a refined, prospective, multicentre study for the Chinese population with strictly defined patient inclusion criteria along with the selection of representative clinical participating centres.

Methods and analysis: This report describes a multicentre, prospective cohort study. As IA is extremely harmful if it ruptures, ethical issues need to be taken into account with regard to this study. Researchers are therefore not able to use randomized controlled trials. The study will be conducted by 12 clinical centres located in different regions of China. The trial recruitment programme begins in 2016 and is scheduled to be completed in 2020. We expect 1500 participants with UIA to be included. Clinical information relating to the participants will be recorded objectively. The primary endpoints are an evaluation of the safety andefficiency of interventional treatment and craniotomy for 6 months after surgery, with each participant completing at least one year of follow-up. The second endpoint is the evaluation of safety and the efficacy of interventional therapy and craniotomy clipping when participants are treated for 12 months. We also address the success of treatment and the incidence of adverse events.

Ethics and dissemination: The research protocol and the informed consent form (ICF) for participants in this study were approved by the ethics committee of Zhujiang Hospital of Southern Medical University (2017-SJWK-001).The results of this study are expected to be disseminated in peer reviewed journals in 2021.

Clinical trial registration number: NTC03133598

Keywords: Un-ruptured aneurysms; Interventional treatment; Craniotomy; Prospective

Strengths and limitations of this study

1. This represents the first prospective cohort study to provide strategies for the selection of treatment options for aneurysm in China, including a number of clinical centers throughout the country, thus, it can fully represent the Chinese population.
2. Inclusion criteria and exclusion criteria are in line with foreign research programs, but have been adopted in the light of China's national conditions to formulate a reasonable research plan, which incorporates an adequate sample size to but ensures that the study can be completed on time.
3. The research process will be coordinated by several departments to ensure the quality and reliability of the research data.
4. The study considers a variety of clinical control factors and the research efficiency

may be reduced as a result.

5. To evaluate the economic benefits of treatment, we considered many factors, after statistical analysis of these factors, the total cost of hospitalization was directly compared, this method may not rigorously reflect the differences in economic benefits.

INTRODUCTION

IA is a common cause of subarachnoid haemorrhage (SAH) that is estimated to affect between 0.2% and 9% of the population. While the detection rate for un-ruptured IAs (UIAs) in healthy people can be as high as 3%, these detection rates differ across various countries.[1] According to recent research, the overall prevalence of UIA was 7.0% in Chinese adults aged 35 to 75 years, with women being more affected than men (8.4% *versus* 5.5%, respectively).[2] In the case of un-ruptured cerebral aneurysms (UCAS), the natural course of UIA varies according to the size, location, and shape of the aneurysm.[3] Interventional therapy and craniotomy represent the two main methods for treating UIAs. However, despite our current knowledge of UIA, and even when we consider information relating to pathological, radiological, and clinical studies, there are no specific criteria that can be used to select the appropriate treatment strategy. Consequently, there is an urgent global requirement to develop methods which will help to select the most appropriate treatment for UIA.[4]

A large number of researchers have investigated the treatment options available for IA and many of these studies have indicated that the postoperative complications associated with interventional therapy are lower than those of craniotomy. However, the short and long-term occlusion rate was lower for interventional therapy than for craniotomy.[5-9] These studies have also highlighted that the size and anatomical location of aneurysms can exert a significant influence on the effect of treatment.[5-9] Interestingly, research failed to identify any significant difference in costs when treatment was compared between endovascular and neurosurgical approaches over the short term.[10] The International Subarachnoid Aneurysm Trial (ISAT) further showed that compared with craniotomy, interventional treatment can clearly improve patient outcome; however, most of the participants in that study had small aneurysms. Consequently, the trial could not definitively conclude that coiling was safer than clipping for all cases of IA.[11-14] While controversial, the ISAT did provide us with a degree of understanding of IA.[15 16]

Previous research has also shown that the risk of IA rupture was 1% to 2%, leading to intracranial haemorrhage, a dangerous condition that is associated with a high mortality and disability rate.[17] However, while UIAs do not generally rupture during long-term follow-up, medical treatment can increase the bleeding rate and the rate of rupture. Thus, in the absence of any specific guidelines for the treatment of aneurysms, the aim of this study was to assess the safety, efficacy and economic benefits of interventional treatment *versus* craniotomy and to propose a scientific strategy for selecting the appropriate form of surgical treatment for UIA that could be deployed

across clinics worldwide.

METHODS AND ANALYSIS

Study design

CIAP is an ongoing, multicentre trial supported by the National Key Research Development Program. CIAP predominantly studies five different aspects of aneurysms: 1) the risk of antithrombotic therapy in patients with UIAs complicated by ischaemic cardio cerebrovascular diseases; 2) the rate of rupture; 3) the risk of rupture and developing a model to predict rupture; 4) treatment options for UIAs and 5) the development of standardized treatments for early stage UIA bleeding. This study dealing with one of the sub-topics is an observational study.

This study evaluates the treatment options for UIAs from the point of view of safety, efficacy and economic benefits, and compares these factors between interventional therapy and craniotomy. The incidence of aneurysms is relatively high among the population, and China is a large country with a wide population distribution. Thus, in order to fully reflect the population more objectively, the researchers will conduct this multicentre, prospective cohort study for five continuous years. Furthermore, referring to previous related research studies and taking into account the characteristics and hazards of UIA，the researchers will not include the random division of participants into groups[3]; a total of 1500 UIA participants are expected to be included. Each participant will be followed up at fixed time points by researchers, and the normal procedures of treatment will not be affected by participants joining the CIAP study. Follow-up data and other clinical information, relating to the participants are recorded in detail, and data are analysed statistically. A concise flow chart of the entire study is shown in Figure 1. The study protocol was approved by the Ethics Committee of Zhujiang Hospital of Southern Medical University (Reference Number: 2017-SJWK-001) and its respective Institutional Review Board (IRB). The trial has been registered at ClinicalTrials.gov with reference number NTC03133598.

Participation centre qualification

To evaluate UIA treatment objectively, it is important to avoid participant bias and to ensure that an adequate number of cases is included in the study. We involved participants in multiple centres at the same time and documented the diagnosis and treatment process in detail objectively. The researchers selected 12 clinical centres (each centre covering more than 2 community or referral units) to conduct this study in collaboration distributed across several regions of China (South east, Southwest, Northwest and Northeast). According to an incomplete dataset, in 2015, a total of 6000 IA patients had been evaluated across the 12 clinical centres. Consequently, the researchers believe that each centre can adequately represent the actual level of IA diagnosis and treatment at a regional and national level. The12 clinical centres used in this study are therefore representative.

There are no specific guidelines for the treatment of UIA. As such, differences exist in

the diagnosis and treatment of IA across different regions, different centres, and even between different neurosurgeons. In this study, the basic requirement of the neurosurgeons who perform surgery on participants is that they are able to complete more than 30 cases of aneurysm surgery per year independently. The study also features an imaging interpretation centre (Internationally Recognized Image Interpretation Laboratory, established by Xuanwu Hospital and the Image Centre of the University of California, Los Angeles, UCLA). This centre is responsible for the unified standard interpretation of imaging data arising from the 12 clinical centres.

Participant selection and screening

The purpose of this study is to recruit patients who are suffering from IA without rupture. First, participants are diagnosed with UIA, either by computed tomography angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA). Patients with fusiform, traumatic, bacterial or dissecting aneurysms, or with SAH of unknown origin, are excluded. These types of patients, involving other vascular diseases (arteriovenous malformation[AVM],arteriovenous fistula [AVF]), malignant tumours, or poor physical condition factors, are expected to live less than a year and are not suitable for study. In order not to disturb the objectivity of the study and to provide good opportunities for follow-up, the researchers also emphasize the ability of participants to live independently (using the modified Rankin scale (mRS) and including those with a score of $\leqslant 3$). Patients are also excluded if they are unable to communicate normally due to serious mental illness; Patients are also excluded if they receive flow diversion as part of their aneurysm treatment(as flow diversion becomes a standard of care for many large, wide-necked aneurysms that are located in the internal carotid artery), if the size of the aneurysm was less than 3 mm, or if aneurysm diagnosis is unclear or difficult. The specific inclusion and exclusion criteria for the trial are provided in Tables 1 and 2, respectively.

The study involves twelve recruiting centres, each of which require IRB approval before recruiting cases. Patients diagnosed with UIA not only receive formal diagnosis and treatment for their aneurysms but also, along with their families, receive full communication from the researchers regarding to the aims of the study. Patients can later voluntarily join the study and sign the ICF. Once these steps are taken, the participant's imaging data will be transmitted to the imaging interpretation centre to re-confirm the diagnosis. If the two diagnoses are not consistent, then the participant is excluded. The participants can withdraw from the study at any time, and the researchers can determine whether the participants continue the study according to their physical status. When serious adverse events occur during the course of the trial, the researchers must terminate the study in advance and report to the ethics committee; adverse events are also entered into the case report form (CRF). This study is an observational study that does not interfere with the normal course of clinical diagnosis and treatment; even if participants withdraw from the study, it will not affect their treatment.

Sample size calculation

Sample size is calculated based on the formula:

$$n = \frac{(z_\alpha \sqrt{(1 + 1/R)\overline{pq}} + z_\beta \sqrt{p_1 q_1 + p_0 q_0 / R})^2}{(P_1 - P_0)^2}$$

(α = 0.05, two-sided test, 80% of the degree of control.)

According to the results of the ISUA test, the mortality rate of the intervention group was 8.7% at one year and that of the craniotomy group was 14.1%, and in the intervention group, it was two times as much in the participants as those in the craniotomy group. We calculated n=1185 (intervention group: n = 395; craniotomy group: n = 790).During the study,20% of the patients would be lost during follow-up, thus, the study requires 1,422participants. Ultimately, we decided to include 1,500 participants.

Data collection

Once participants are included in the study, all information regarding the course of diagnosis and treatment are recorded in the CRF-A. This study also uses an electronic data collection system (EDC) developed by the National Centre for Cardiovascular Diseases; information stored on CRFs is entered into the EDC by a designated person on each site, and each site shares data with the EDC. The objective of this study is to objectively compare the safety, efficacy and economic benefits of the two treatment methods for UIA, and each participants is followed for at least one year (at 3, 6, and 12 months). Consequently, each participant will have at least one year of follow-up data, and when the study is finished, participants will be followed at least once a year up to 5 years. All participants undergo DSA at 18 months. Follow-up data will be acquired by a neurosurgeon either by telephone or by social tools as soon as possible and recorded in the CRF-B. In most cases, DSA examination should be conducted six months after the operation to confirm the effect of treatment, which is the vital end point of this study. Furthermore, data acquired at three and twelve months after surgery are also an important aspect of the study. A detailed follow-up plan is given in Figure 2. During the study, the researchers will be obliged to protect the personal privacy and medical information of each participant, and strictly adhere to ethical guidelines.

Data management

As all data will be collected using CRFs and the EDC, the CIAP have established a data management committee (DMC, located in Xuanwu hospital) to supervise data quality and have hired a specialist data management company responsible for constructing the EDC and ensuring data security, integrity and accuracy. Before the participants are formally enrolled, the DMC will hold CRF and EDC data entry study

classes for the main studies in each collaboration clinical centre regarding data entry, modification and retrieval, and setting permissions for the main researchers in the EDC. A clinical research operator (CRO) supervises project progress and quality of data implementation, and the researcher assigned. The clinical research associate (CRA) will regularly visit each participating centre to ensure that all contents of the research programme are strictly followed. If not, the CRA promptly submits information to the investigators. Throughout the project, a research summary conference will be held every 6 months to discuss progress and solve any problems that may arise. This study holds a study summary meeting every 6 months to discuss and solve research question and outcome measures informed by patients' priorities, experience, and preferences.

Data analysis

The Department of Medical Statistics at the National Centre for Cardiovascular Diseases will be responsible for all data management and statistical analysis. SPSS V21.0 statistical software (IBM Corp, Armonk, New York, USA) will be used to analyse the results, with normally distributed data being represented by $\bar{x}$ ±SD. Skewed distribution data will be described by the median (*M*) and the four-quartile range (*P25; P75*) using an independent t test or rank sum test. Categorical variables will be described by frequency, percentage and grouped data, andrate or percentages between the groups will be compared with the Chi-square test or by the Fisher exact test. Rank data will be analysed by the rank sum test. $P<0.05$ will be considered to indicate statistical significance.

Endpoints of the study

The endpoints of the study have also been divided into primary and secondary endpoints. The safety and efficacy of interventional treatment and craniotomy are considered as the primary endpoint of the study and represent the key goals of investigators. Using participant mortality and morbidity rates to evaluate the safety of interventional and craniotomy, and by considering ipsilateral stroke and neurological deficits within 30 days, we shall enhance the safety evaluation of our study, and these features will play a positive role in our findings. Efficacy will be evaluated by aneurysm recurrence rate, re-bleeding rate and complete occlusion rate. The secondary endpoint mainly considers the time of postoperative evaluation and the occurrence of adverse events. The primary and the secondary endpoints are described in Table 3.

Methods of evaluating the economic benefits of treatment

The study combines the following three aspects of patient evaluation in terms of the economic benefits of treatment: admission(GCS, WFNS, mRS, MMSE), the third day after surgery (GCS, WFNS, mRS, MMSE) and the total cost of hospitalization. Multivariate logistic regression analyses will be used to adjust for GCS, WFNS, mRS, MMSE(admission and the third day after surgery),and then to compare the total cost of hospitalization for both treatments with control of other economic factors, such as

length of ICU stay, length of hospital stay, readmission rate, drug changes, adverse events, intraoperation complications and postoperative complications, etc..

Ethics and dissemination

The study was approved by the China's Ministry of Science and Technology as a national key research programme in 2016. During the research process, the investigators strictly followed the Declaration of Helsinki and Human Biomedical Research Ethical Issues. Participants will not be affected the normal course of clinical diagnosis and treatment of aneurysms because of participating in the study. Professor Chuanzhi Duan is the principal investigator who will supervise the successful implementation of the study. The results of this study will be disseminated in peer-reviewed journals in 2021.

Patient and Public Involvement

Patients or the public were not directly involved in the study design or conduct of the study. When the participants were included, we told them that this study will take about 5 years to complete and after the results of the study are published, we will inform them by telephone immediately.

DISCUSSION

To the best of our knowledge, CIAP is a project exploring the characteristics of intracranial aneurysms nationwide among the Chinese people and does so from a range of different aspects: the rate of spontaneous aneurysm rupture; risk factors of rupture; and the emergency treatment required for ruptured aneurysms; etc. In particular, this study compares two different treatment methods for UIA. IA is a common cause of SAH, but this does not imply that if the SAH rate is high, the incidence of IA is therefore also high;[18] to a certain extent, SAH can lead to an erroneous understanding of IA. Consequently, we should exclude the unknown causes of SAH.[19] DSA has traditionally been considered the gold standard for detecting aneurysms. However, combined with existing data, the present study suggests that the incidence of UIA within the population varies according to the method of examination. The main reason for this finding is that the accuracy of different diagnostic methods is affected by the size of aneurysms. Studies have shown that the sensitivity of DSA is only 85% for small aneurysms (<3 mm) and that the efficacy of computed tomographic (CT) angiography for diagnosing intracranial aneurysms is increasingly being recognized;[1 20-23] this study excludes patients with small aneurysms and in doing so increases the accuracy of the study. However, this finding means that the study can be considered to be incomplete, as it only targets aneurysms of a certain size.

The treatment of IA cannot be separated from interventional treatment and craniotomy. Interventional therapy is becoming increasingly popular among neurosurgeons, but selecting which of the two approaches to use for treatment has been controversial.[24-26] Most scholars believe that interventional therapy is associated with lower mortality than is craniotomy; the recurrence and re-bleeding rate of interventional therapy is

higher,[12] and combined with other techniques, interventional therapy may achieve better results.[5 27 28] The recurrence rate of interventional therapy is higher because for certain types of aneurysms, such as wide neck aneurysms, the treatment effect is not satisfactory. However, as the intervention materials and technology improve, many scholars have adopted this approach for the treatment of aneurysms and have obtained good results. [29-33] Comparing the two methods in terms of safety and efficacy, it is necessary to consider a range of factors, including age, gender, subarachnoid haemorrhage and aneurysm size because these are the principal factors which can influence the re-bleeding of aneurysms.[34 35] Surgery can cause haemodynamic changes in an aneurysm, but there is no conclusive evidence to show that this plays a positive role in the recurrence of aneurysms; the study does not take into account the effects of haemodynamics on the results,[36 37]but rather, the researchers, with the help of a professional statistical team, can try to minimize the impact of baseline data differences upon the results.

The authors believe that the most obvious limitations of this study are the following. First, we have included many factors in order to fully evaluate the economic benefits of treatment. Although there are statistical methods to address these factors, error still exists, and directly comparing total hospital costs, this method may not be highly rigorous. Second, in the study process, there are many factors affecting outcome, including treatment time, drug changes and adverse events, etc. Investigators primarily use retrospective methods to record these data, and the research method is single, resulting in convincing evidence that needs improvement. In addition, our study includes 1,500 participants. Whether this sample accurately represents the Chinese patients with IA is unknown. There are no national studies to indicate the overall incidence of IA in China, and we can only refer to the existing literature. CIAP sub-project 1 aims to indicate the incidence of IA in China.

With careful research design, it is possible to consider and exclude the factors that could potentially influence the results, and by referring to foreign research programmes, this study may provide helpful information for therapeutic strategies for UIA in clinical practice. Results from this study may provide us with a chance of using normative interventions for UIA before deploying interventional treatment and craniotomy, thereby providing significant benefit for patients with aneurysms.

Contributors

CD obtained the research funding and is the principal investigator of this study. YC, HF, XL, MH, YQ, XY and HZ have developed the study protocol and YC is the main author of this article. HF, XH, SG and XL have revised the manuscript. XS, LW, ZW, XT, MZ, MA and ZT are the main people responsible for the seven clinical centers and responsible for implementing this study. CD has approved publication of the final manuscript. YC, HF, XS, LW, ZW, XT, MZ, MA and ZT are thanked for they role in the recruitment of patients.

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Conflict of interest
None declared

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Table 1. Inclusion criteria.

1. At least 1 intracranial un-ruptured aneurysm confirmed by imaging(CTA/MRA/DSA), whether or not there are clinical symptoms
2. For patients with multiple aneurysms, the treatment interval is 6 months, regardless of whether they have been treated or not
3. Patients currently have the ability to live independently and have an mRS scale score of ⩽3
4. Age is > 14 years old
5. Patients or family members agree to provide informed written consent

Table 2. Exclusion criteria.

1. Intracranial aneurysms associated with unexplained subarachnoid hemorrhage for 30 days
2. Patients with other intracranial vascular malformations, such as AVM or AVF
3. Patients with intracranial or other parts of the body suffering from malignancy
4. Fusiform, traumatic, bacterial, or dissecting aneurysms
5. Patients with severe mental illness who are unable to communicate when disease is diagnosed
6. Patients with poor overall state, expected survival time less than 1 year or poor physical status, cannot tolerate general anesthesia or aneurysm surgeries
7. Patients involved in other clinical studies of intracranial aneurysms
8. Patients undergoing surgical clipping or endovascular treatment simultaneously
9. Patients who receive flow diversion as aneurysm treatment
10. Patients who refused to follow up
11. The size of the aneurysm ⩽ 3 mm

CTA: computed tomography angiography; MRA: magnetic resonance angiography; DSA: digital subtraction angiography; AVM: arteriovenousmalformation; AVF: arteriovenous fistula; mRS: modified Rankin scale

Table3.endpoints of the study

1. The primary endpoint

①The main security endpoint:

The safety evaluation of interventional therapy and craniotomy clipping when the participants are treated for 6 months: including participants' mortality (mRS = 6), morbidity (3 ⩽ mRS ⩽ 5 points);the emergency of ipsilateral stroke and neurological deficits within 30 days are also recognized as reliability measures to evaluate the security of interventional and craniotomy.

②The main effectiveness endpoint:

The effectiveness evaluation of interventional therapy and craniotomy clipping when the participants are treated for 6 months: including the recurrence(Raymond classification=1) rate and complete occlusion (Raymond classification=1) rate of aneurysms,re-bleeding rate of subjects.

2. The secondary endpoints

① The safety evaluation of interventional therapy and craniotomy clipping when the participants are treated for 12 months: including participants ' mortality (mRS = 6), morbidity (3 ⩽ mRS ⩽ 5 points);

② The effectiveness evaluation of interventional therapy and craniotomy clipping when the participants are treated for 12 months: including the recurrence(Raymond classification=1) rate and complete occlusion (Raymond classification=1) rate of aneurysms,re-bleeding rate of subjects;

③The success rate of treatment;

④The success rate of 6 months after interventional therapy or craniotomy clipping(the DSA hint:aneurysm completely or nearly total occlusion, re-canalization or re-growth did not appear);

⑤The incidence of major adverse events during hospitalization;

⑥The incidence of major adverse events after 3months of surgery;

⑦The incidence of major adverse events in 3months and 6months later after operation;

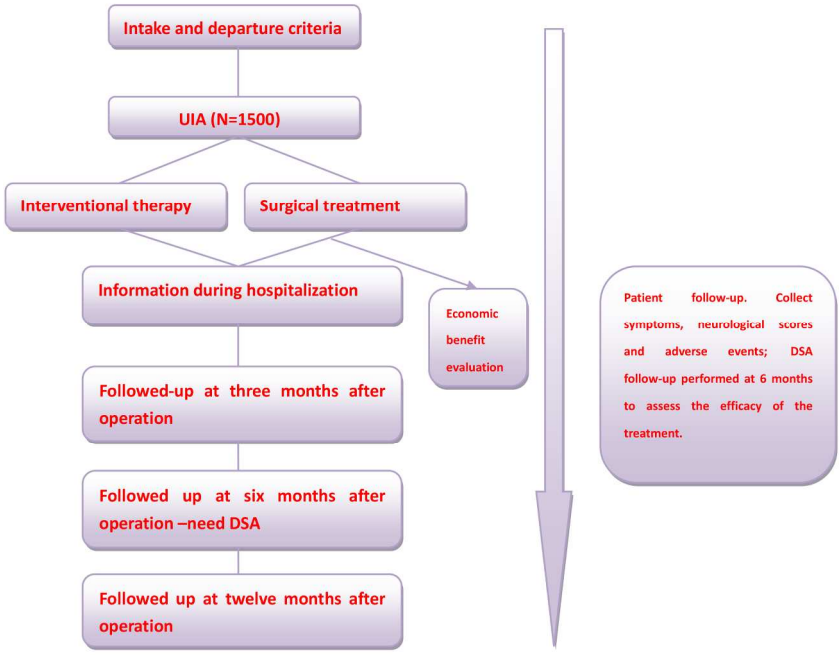
⑧The incidence of major adverse events in 6months and 12months later after operation.

Figure legends

Figure1.Research flowchart

Figure2. Participants visit and evaluation schedule

Figure 1. Research flowchart:



UIA: un-ruptured aneurysms; DSA: digital subtraction angiography

169x243mm (300 x 300 DPI)

Figure 2. Participants **visit and evaluation schedule.**

	Screening period	Treatment period		follow-up period		
Visit number	**1**	**2**	**3**	**4**	**5**	**6**
Study	**Preoperative screening**	**In operation**	**Before discharge**	**3 months±14 days**	**6 months±30 days**	**12 months±30 days**
informed consent	√					
Intake and departure criteria	√					
Baseline information	√					
The history and history of drug	√					
Therapeutic drug	√		√	√	√	√
Symptoms and physical examination	√		√	√	√	√
electrocardiogram	√					
Routine blood test	√			√	√	√
Blood sugar	√			√	√	√
Blood lipid	√			√	√	√
Homocysteine	√					
Head CT/MRI	√		√		√	
Vascular Ultrasonography	√					
CTA/MRA/DSA	√				√	
mRS score	√		√	√	√	√
GCS score	√		√			
WFNS score	√					
MMSE score	√		√	√	√	√
Total operating cost			√			
Adverse event		√	√	√	√	√

GCS: Glasgow Coma Scale; WFNS: The World Federation of neurosurgeons; MMSE: mini-mental state examination

210x297mm (300 x 300 DPI)