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Protocol

Ginkgolide in Ischmic Stroke patients with large Artery Atherosclerosis(GISAA):A randomized, double-blinded, multicenter, placebo-controlled study

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Abstract

Introduction: Intracranial stenosis in ischemic stroke is a major medical challenge in China. Large atherosclerotic ischemic stroke is the most common type of cerebral infarction. Ginkgolide is one of potential neuroprotection agents in stroke patients, Preclinical studies have demonstrated that it improves outcomes in patients with stroke with low rate of any adverse events. The efficacy and safety of ginkgolide in stroke patients with large artery atherosclerotic are still unspecified. Method: GISAA is a randomized, double-blinded, multicenter, placebo-controlled of Post marketing clinical study. A total of 878 Chinese patients with Large atherosclerotic ischemic stroke will be enrolled. All patients receive ginkgolide/ placebo by intravenous drip once daily for 14consecutive days. Primary outcome includes the recurrence stroke rate and mortality rate. Secondary outcomes include functional improvement measured by the National Institutes of Health Stroke Scale, Barthel index and modified Rankin Scale. Moreover, the platelet aggregation rate would be measured as the concentration of PAF, TXA2, and ADP. Discussion: The ongoing Ginkgolide in Ischemic Stroke patients with large Artery Atherosclerosis(GISAA)trial is designed to evaluate the efficacy and safety of Ginkgolide in Chinese patients with Large atherosclerotic ischemic stroke.Data from large-scale clinical studies are still unavailable concerning the post-marketing use of ginkgolide. Trial Registration: The study has prospectively registered on www.chictr.org.cn(ChiCTR-IPR-17012310).

Keywords: atherosclerosis, ischemic stroke, ginkgolide, protocols, post marketing clinical study

Background

The Global Burden of Disease 2013 study shows that although stroke incidence, prevalence, mortality, and disability-adjusted life-years rates tend to decline from 1990 to 2013, the absolute number of people who have a stroke every year, stroke survivors, related deaths, and the overall global burden of stroke are great and increasing, particularly in low-to-middle income countries [1]. In China, stroke is the second leading cause of death, and ischemic stroke is the most common stroke subtype. According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST), stroke is classified into large artery atherosclerotic type, cardiogenic cerebral embolism, small artery block type, lacunar stroke, other causes and ischemic stroke of unknown cause. Tsai CF et al reported that the proportion of strokes due to Large Artery Atherosclerosis (LAA) ranged from 12% to 54%, small vessel disease 20% to 42%, cardioembolism 10% to 26%, and the combination of other specific determined and undetermined etiology subtypes 4% to 34% [2]. Of all ischemic strokes, LAA of the head and neck is responsible for approximately 15% of stroke [3]. However, LAA is the leading stroke subtype in China[4]. In many Asian countries, LAA often affects the middle cerebral artery, intracranial portion of the internal carotid artery, and vertebrobasilar artery, which is estimated to 33%-50% of stroke in Chinese stroke populations [5]. The risk of early recurrent stroke is high in those patients with LAA. It has been reported that the risk of recurrent stroke might be as

high as 8-12% in the first 7 days, [6] and 12%-14% during a 2-year follow-up, [7] even with the standard therapy. The annual risk may exceed 20% in stroke patients with LAA [7]. Carotid endarterectomy and stenting are both effective at reducing risk of recurrent stroke in patients with extracranial carotid, while limited intervention was warranted to be done in patients with intracranial artery stenosis.

As known, platelets have a crucial role in triggering arterial thrombosis [8] and in promoting atherogenesis [9], and also play a critical role in the pathogenesis of ischemia stroke. Microembolic signals are common in patients with LAA [10] and are an independent marker of recurrent stroke [11]. As a result, clinical guidelines recommend antiplatelet therapy for patients with non-cardioembolic stroke [12]. Not only does antiplatelet therapy decrease the risk of recurrent stroke, but reduce the risk of neurological deterioration.

Previous animal study showed that ginkgolide injection could antagonism PAF-induced platelet aggregation, inhibits the activation of platelets, and is a kind of important antiplatelet aggregation drug [23]. Data in animal study have suggested that ginkgolide injection combined with aspirin, clopidogrel could produce cooperative effects to prevent PAF-induced platelet aggregation. [24] We hypothesize that their combination may have additive effects on platelet. Clinical studies have demonstrated the efficacy of ginkgolide injection in the treatment of ischemic stroke, and it can effectively improve the outcome of stroke patients [25,26]. Herein, we planned to perform a randomized, double-blinded, multicenter, placebo-controlled trial, which evaluated the effects of combined ginkgolide and aspirin therapy relative to aspirin monotherapy on clinical outcome and platelet activation in ischemic stroke patients with LAA.

Objective

The GISAA trial is to evaluate the effect of Ginkgolide in reducing clinical outcome in Chinese patients with large artery atherosclerotic ischemic stroke.

Design

GISAA is a randomized, double-blinded, multicenter, placebo-controlled trial (Figure1). Patients enrollment planned to begin at 50 stroke centers across China from May 2016. The planned enrollment is 878 patients with ischemic stroke involving large-artery stenosis. The present study was approved by the central ethics committee at the leading study center at Huashan Hospital, Fudan University and by all the ethics committees at all participating sites. Informed written consents were planned to obtain from patients or their legal surrogates. The study performs followed the provisions of the ICH Good Clinical Practice (GCP) and the Declaration of Helsinki.

Study Population and Allocation

The inclusion and exclusion criteria of patients are summarized in Table 1. Randomized block was used to allocated patients and the random allocation scheme 1:1 treatment group and control group, was made by using SAS9.1.3 software. The generate random encoding by using randomized method, block selection and the length of the random initial value parameters such as seeds of confidential data are sealed together in blind bottom. Patients were also stratified by their baseline severity and risk factors. According to this random number, the drug is coded by the person who has nothing to do with the test. Each clinical research center was allocated according to the assigned drug number and selected according to the case order. There were two copies of blind bottom, which were respectively located in Department of Neurology, Huashan Hospital, Fudan University and Chengdu hundred pharmaceutical co. Ltd.

Table 1. The Inclusion/ exclusion criteria of GISAA

Inclusion criteria:

1. Consistent with the diagnostic criteria for ischemic stroke;
   Diagnostic criteria:
   ① Acute onset
   ② Focal neurological impairment (unilateral face or limb weakness or numbness, language, etc.); a small number have general neurological impairment
   ③ Symptoms and signs last for hours or more
   ④ Brain CT or MRI ruled out intracerebral hemorrhage and other lesions
   ⑤ Brain CT or MRI showed a major infarction lesion
2. MRA or CTA showed atherosclerotic cause carotid artery, anterior cerebral artery, middle cerebral artery, posterior cerebral artery or vertebrobasilar artery stenosis;
3. onset in 72h;3< NIHSS score≤25;
4. First onset, or past onset, not associated with serious sequelae;
5. Voluntary consent of informed consent.

Exclusion criteria:

1. Transient ischemic attack;
2. Patients who have been or are scheduled to be treated with thrombolysis;
3. Imaging showed patient with cerebral hemorrhage;
4. Patients with cerebral hemorrhage and cerebral arteritis after cerebral infarction;
5. Brain embolism caused by atrial fibrillation, brain tumor, brain trauma, brain parasitic disease, rheumatic heart disease, coronary heart disease and other heart diseases;
6. Liver dysfunction (ALT/AST≥2× upper limit of normal [ULN]), renal dysfunction (Cr >1.5 × ULN);
7. Bleeding tendency, severe bleeding occurred within 3 months, PLT< normal range/APTT> ULN of more than 3 seconds;
8. Patients treated with double resistance;
9. Allergic to ginkgo, alcohol, glycerin;
10. Women during pregnancy and lactation period or plan to be pregnant;
11. Participants in other clinical studies for the last 1 months;
12. Other conditions making it inappropriate to participate in this clinical study in the investigator's opinions.

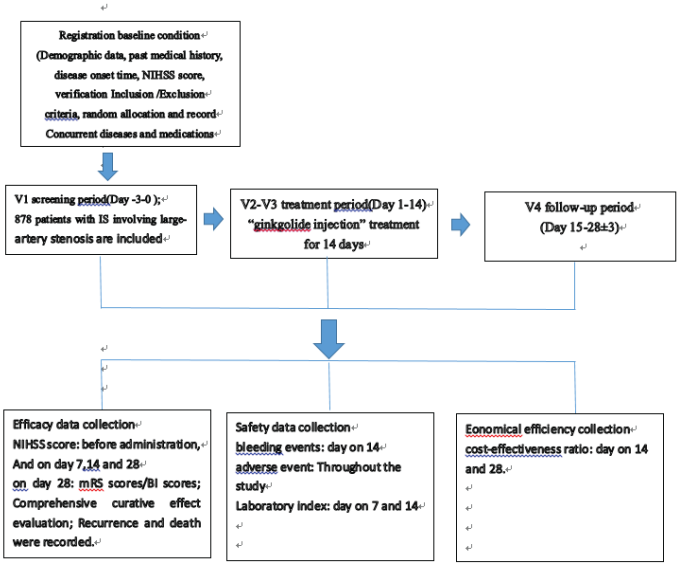

Figure 1. Overview of study design of GISAA study.

Sample Size Estimates

The sample size of this study is estimated based on rate of recurrence stroke, mortality within 28 days in the Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR) study [27]. Using PASS11.0 software to calculate the sample content, we used threshold value as 0.010 with α=0.025(unilateral side) and β=0.20. We derived the expected sample size of this study accordingly is 732 samples, 366 samples in each group. Considering the possibility of dropout during clinical trials an increase of 20% based on the estimated value of sample size formula, the total sample size was 878 with 439 cases in each group.

Taking into account the number of patients in the GISAA trial and incidence of ischemic stroke patients with LAA in China, we plan to complete the trial in two year. Between May 2016 and Dec 2018, 878 patients will be randomized (439 in the ginkgolide plus aspirin group and 439 in the aspirin plus placebo group) at 43 centers in China.

Interventions

Patients were screened after inclusion of exclusion criteria. All patients met the inclusion criteria were randomly assigned to receive aspirin 100mg oral daily combined with intravenous ginkgolide 10ml for 14 days or aspirin 100mg oral daily combined with placebo. Intravenous ginkgolide and placebo were labeled with same drug label, and the drug was identical in appearance.

During the present study, anticoagulants, any other thrombolytic drugs, Chinese traditional medicine for promoting blood circulation to dissipate blood stasis and apoplexy treatment, and other antiplatelet aggregation drugs other than aspirin are prohibited. Treatment of combined diseases, such as antihypertensive drugs, hypoglycemic drugs, lipid-lowering drugs and so on were allowed to be used followed by the physician recommendations. The detailed follow-up schedule of study is shown in Table 2.

Outcome

The rate of stroke recurrence and mortality were followed-up within 28 days after randomization [28]: Recurrent stroke were defined as an index event (ischemic or hemorrhagic) after 24 hours of randomization or NIHSS increasing more than 4 points. Ischemic stroke was defined as an acute focal infarction of the brain or retina with one of the following: sudden onset of a new focal neurologic deficit, with clinical or imaging evidence of infarction lasting 24 hours or more and not attributable

Table 2 . The study workflow of GISSA assessments

Item	Period			
Visit	Screening period	Treatment period		Follow-up period
Time	1 Day -3~0	2 Day 7	3 Day 14±3	4 Day 28±3
Signing informed consent form	X			
Demographics	X			
Past history/treatment history	X			
Inclusion/exclusion criteria	X			
Blood routine/ Urine routine	X		X	
Stool routine + occult blood	X		X	
liver / Renal Function / blood sugar	X		X	
electrocardiogram	X		X	
Blood/urine. pregnancy test	X		X	
MRA	X		X	
Coagulation function	X	X	X	
PAGT(PAF/ADP/ TXA2)	X	X	X	
Coagulation factor concentration	X	X	X	
(PAF/ADP/TXA2)	X		X	
Evaluation of bleeding events				
NIHSS scores	X	X	X	X
mRS scores				X
BI index scores				X
Investigational drug management	X		X	X
Recurrence/death				X
Patient treatment cost record			X	X
Concomitant. medication	X		X	X
Adverse events	X	X	X	X

to a nonischemic cause (i.e., not associated with brain infection, trauma, tumor, seizure, severe dynamic disorders, or degenerative neurologic disease);a new focal neurologic deficit lasting for less than 24 hours and not attributable to a nonischemic cause but accompanied by neuroimaging evidence of new brain infarction; or rapid worsening of an existing focal neurologic deficit lasting more than 24 hours and not attributable to a nonischemic cause, accompanied by new ischemic changes on MRI or CT of the brain and clearly distinct from the index ischemic event. Hemorrhagic stroke was defined as acute extravasation of blood into the brain parenchyma or subarachnoid space with associated neurologic symptoms.

We assessed two aspects of secondary clinical outcome. (1) The improvement of clinical symptoms measured by National Institute of Health stroke scale (NIHSS) score at 14 and 28 days after randomization. (2) The improvement of functional outcome assessed by modified Rankin scale score (mRS) at 28 days after randomization.

The NIHSS is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, ranged from 0 to 42 points. For each item, a score of 0 typically indicates normal function in that specific ability, whereas a higher score is indicative of some level of impairment. The individual scores from each item are summed to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum of 0.

The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke. The scale runs from 0 to 6, running from perfect health without symptoms to death.
0: No symptoms.
1: No significant disability: able to carry out all usual activities, despite some symptoms.
2: Slight disability: able to look after own affairs without assistance, but unable to carry out all previous activities.
3: Moderate disability: requires some help, but able to walk unassisted.
4: Moderately severe disability: unable to attend own bodily needs without assistance, and unable to walk unassisted.
5: Severe disability: requires constant nursing care and attention, bedridden, incontinent.
6: Dead.

Huashan Hospital were responsible for training all assessment and measurements, and all researchers need to have a certificate of training before their first patient enrollment.

Patients platelet aggregation rate was induced by PAF, TXA2, and ADP, at baseline (-3 days-0 days), 7days and 28 days after randomization, respectively. Central Laboratory were in charge of testing their platelet aggregation rate with standard protocol.

The incidence of bleeding events (radiographic examination combined with bleeding symptoms) and adverse events in the two groups.

Data Quality Assurance and Control

The case report forms would be filled out by the researchers, and each case must be completed with a case report form. The case report form by the clinical research assistant (CRA) examination, give the data administrator for data entry and management work. Data administrator establishes recorded data storage by EpiData 3.0 software. In order to ensure the accuracy of the data, the clinical research centers and Data Administrators independently carry out double entry and proofread. The clinical research center of the data administrator is responsible for the audit quality of the case report form, review of qualified data must be complete entry and upload to the Internet within a week. If there is any doubt, requirement table was built up and questions would be raised to researchers by the CRA. All researchers should response to questions as soon as possible. Data administrator according to the researcher's answer for data validation and input.

After confirming that the database was established correctly, the data were locked by the principal researcher, the applicant, and the statistical analyst. The locked data file is no longer altered.

Statistical Analyses

The statistical analyses are performed by Department of Epidemiology and Health Statistics, Huaxi School of Public Health, Sichuan University. Analysis of continuous variables will be described by Student's t test. For the analysis of (co)variance or in case of skewed distributions which cannot be normalized by log transformation, corresponding nonparametric tests will be used. Chi-squared test will be used for analysis of categorical variables and logistic regression analyses will be used to adjust for potential confounding factors.

Quality Control and Data Storage

To ensure the supervision of clinical research quality control and measurement, researchers should agree to all research data preservation, including confirmation of subjects (can effectively check the record data, such as case report forms and hospital original records). The preserve time is 5 years.

All patients' information of this clinical study belongs to the researchers. The Research Committee is responsible for all clinical research implication, interpretation and data reporting.

Role of the Funding Source

All interventions and placebos were sponsored by

Chengdu hundred pharmaceutical co. Ltd. Otherwise, the sponsor does not play a role in the study design, data collection, data analysis, data interpretation, or data reporting. The members of Data and Safety Monitoring Board were selected by the research committee, were in place to ensure the safety of patients during the study, with predetermined periodic assessments of safety and terminate rules.

Discussion

The neuroprotection of ginkgolide has been published, however, the ginkgolide combined with aspirin in acute ischemic stroke with LAA was unclear. We hypothesis that the combination of ginkgolide and aspirin can reduce the recurrence stroke rate and mortality, compared to aspirin alone in patients with LAA.

Except the clinical benefit, GISAA trial also explores the relationship between the level of platelet activation and neurological deterioration. We hypothesize that the platelet aggregation induced by PAF, TXA2 or ADP would be lower in patients who does not have subsequent neurological deterioration and recurrent stroke.

It is common that LAA patients were commonly worsening and more likely to recurrent, even with aspirin, which is the widely used and reduces stroke risk by 18% [13]. On the other hand, the present data suggested that aspirin non-responder status was need to considered as suspected in approximately 30–40 % of patients with recurrent cerebrovascular ischemic events despite regular use of aspirin [14].The 2-year recurrent ischemic stroke rates are 19.7% in stroke patients with LAA, in spite of aspirin therapy [15].Therefore, combination therapy might be helpful to reduce the incidence of recurrent ischemic stroke or neurologic deterioration. However, combination treatment with aspirin and anticoagulation (warfarin/low-molecular-weight heparin) was also no more effective than aspirin alone in preventing recurrent stroke or reducing neurological deterioration [16-18]. Combined antiplatelet therapy is supposed to be more clinical benefit compared with aspirin and placebo. The CHANCE (Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events) trial and a following meta-analysis showed that clopidogrel plus aspirin versus aspirin alone initiated in early period significantly reduced risk of recurrent stroke with no increase in major hemorrhage [19,20].

However, The COMPRESS (Combination of Clopidogrel and Aspirin for Prevention of Recurrence in Acute Atherothrombotic Stroke Study) trial showed that patients with acute ischemic stroke of presumed LAA origin within 48 hours of onset, adding clopidogrel to aspirin for 30 days compared with aspirin alone did not reduce the risk of developing new ischemic lesions, clinical stroke recurrence, composite major vascular events, and functional disability [21].The main reasons of these debating results are that CHANCE enrolled patients are within 24 hours of onset and COMPRESS did not use a clopidogrel loading dose because of safety concerns. The ginkgolide, as a safety and effective therapy, might be benefit for acute stroke patients with LAA. Our GISAA trial would provide an evidence that the ginkgolide combined with antiplatelet therapy has a potential benefit in patients with an ischemic stroke with LAA in short term treatment.

Abbreviations

GISSA: Ginkgolide in Ischmic Stroke patients with large Artery Atherosclerosis; TOAST: Trial of Org 10172 in Acute Stroke Treatment; GCP: Good Clinical Practice; CHANCE: Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events; COMPRESS: Combination of Clopidogrel and Aspirin for Prevention of Recurrence in Acute Atherothrombotic Stroke Study; LAA: Large Artery Atherosclerosis; CRA:clinical research assistant; NIHSS: National Institute of Health stroke scale; CLAIR: Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis

Ethics Approval and Consent to Participate

Huashan Hospital IRB has approved this study protocol.

Consent for Publication

Not available

Availability of Data and Material

Not available

Competing Interests

All interventions and placebos were sponsored by Chengdu hundred pharmaceutical co. Ltd. Otherwise, the sponsor does not play a role in the study design, data collection, data analysis, data interpretation, or data reporting. There is no other conflict of interest.

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All interventions and placebos were sponsored by Chengdu hundred pharmaceutical co. Ltd.

Authors' Contribution

Qiang Dong designed and draft the protocol. GISAA research committee includes Dr. Liu Ming from West China Hospital, Dr. Yi Yang from the first hospital affiliated to Jilin University, Dr. Yun Xu From Gulou Hospital, Dr. Xin Wang from Zhongshan Hospital affiliated to Fudan University, Dr. Fan Jun from 202 Hospital, Dr. Bo Xiao from Xiangya Hospital Central South University, Dr Linhong Feng from the first hospital affiliated to Harbin Medical University, Dr Anding Xu from the first hospital

affiliated to Jinan University. They have participated and approved the protocol after revision.

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Not available.

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