Clinical Evidence-Based Evaluation of ZFXNY in Treatment of Acute Cerebral Infarction

Wei Hu

Chengdu University of Traditional Chinese Medicine Affiliated Hospital <https://orcid.org/0000-0002-2524-1164>

Chenhui Zhang

Hospital of Chengdu University of Traditional Chinese Medicine

Hong Zhang (✉ E-zhanghong1874@163.com)

Hospital of Chengdu University of Traditional Chinese Medicine

Study protocol

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Abstract

Background: Stroke is a severe and life-threatening disease, owns high rates of disability and mortality.^[1] Stroke and ischemic heart disease, chronic obstructive pulmonary disease are the world's three main killers. Ischemic strokes account for the vast majority of strokes.^[2] Modern medicine has some advantages in treating ischemic stroke, but there are also limitations. Traditional Chinese medicine has thousands of years of experience in treating stroke, but there are few high quality clinical Randomized controlled trial.

Methods: This is a multicenter, randomized, double-blind, placebo-controlled trial. 286 patients were randomly divided into test group and Control Group. Both groups received General Western medicine treatment, the test group combined with Chinese medicine treatment, the control group combined with placebo treatment. The duration of treatment was 30 days and the follow-up was 90 days. evaluation indicators include: Modified Rankin Scale, NIH stroke Scale, Glasgow Coma Scale, Barthel Index, Case fatality rate. Laboratory specifications and safety assessments will also be taken into account.

Discussion: The aim of this study was to evaluate the safety and efficacy of ZFXNY in the treatment of acute cerebral infarction. Our research will provide a reliable evidence-based medicine basis for the treatment of acute cerebral infarction with traditional Chinese medicine, and provide another option for the treatment of acute cerebral infarction.

Trial registration: ChiCTR2100043796, Registered February 28th, 2021.

Introduction

Acute ischemic stroke is one of the main diseases causing disability and death in human being.^[3] To date, stroke is the world's 2nd leading cause of death, responsible for approximately 11% of total deaths. The incidence of the disease remains high in developing and developed countries as a result of rising living standards^[4]. (<https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>) Acute ischemic cerebral apoplexy (ACI) is the most common type of apoplexy, accounting for 69.6%-70.8% of cerebral apoplexy in China.^[5] In recent years, the mortality of hospitalized patients in China with acute cerebral infarction is about 2.3%-3.2% one month after onset^[6,7], after three months the case fatality rate was 9%-9.6% , the death/disability rate was 34.5%-37.1% , the one year case fatality rate was 14.4%-15.4% , and the death/disability rate was 33.4%-33.8%.^[8] ACI has the characteristics of high incidence, high recurrence rate, high disability rate and high mortality. Over the past year, the ACI has had a tremendous impact on the lives of people around the world and placed a heavy burden on the global health system.

Two effective treatments for acute cerebral infarction are endovascular therapy and intravenous thrombolysis in modern medicine. But both treatments are highly time-dependent.^[3,9,10] Due to the limitation of time and contraindication, there are still a large number of patients who can not use these

two methods. Other basic treatments mostly medicine cost a long time and have side effects. In particular, long term use of Antiplatelet drug or anticoagulants can increase the risk of bleeding.

Except of modern treatment, TCM is a treatment for widely use in Asia with a thousands of years of historical experience. Pharmacological studies have demonstrated some TCM to have anti-inflammatory, antioxidant, protecting the blood-brain barrier and protective effects against ischemia and reperfusion injury.^[11,12,13] In the numerous traditional Chinese medicine treatment, the benefit qi and invigorate the blood treatment effect is the best.^[14] ZFXNY is a preparation in Hospital of Chengdu university of Traditional Chinese Medicine. It was formulated by Professor Shaohong Chen according to benefit qi and invigorate the blood treatment. The main components of ZFXNY are: Panax Notoginseng, safflower, Salvia Miltiorrhiza, Chuanxiong, Rhubarb. These ingredients have been proven effective in treating acute cerebral infarction.^[15,16] The drug has been used for more than 30 years and has achieved good curative effect. This project intends to carry out prospective, multi-center evidence-based research to verify the curative effect of ZFXNY, and provide high-quality evidence for the treatment of ischemic stroke.

Design

This study was a prospective, multicenter, randomized, double-blind, placebo-controlled trial. The center of research participation includes 4 medical institutions in China: The Affiliated Hospital of Chengdu University of TCM, The Affiliated Hospital of North Sichuan Medical College, The Affiliated Hospital of Southwest Medical University, The Guangyuan Hospital of TCM. The trial has been registered in the China Clinical Trial Registration Center.

To prevent design bias, we will follow the Consolidated Standards of Reporting Trials statement^[17] and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement.^[18] This trial will include 286 participants, and the participants will be informed of the benefits and risks of the study in detail. After obtaining written informed consent, eligible participants will be randomly assigned to the ZFXNY group and control group in a ratio of 1:1. The entire study includes a screening assessment period, a 30 days treatment period, and an 90 days follow-up period. The schedule of enrollments, interventions, and assessments is shown in Figure 1 (the SPIRIT figure). The illustration of the design for clinical studies is presented below in Figure 2. The SPIRIT 2013 checklist is presented in Additional File 1.

Ethics approval

This study abides by the Declaration of Helsinki (Edinburgh, 2000). The research program has been approved by the China Ethics Review Committee for Registered Clinical Trials (Approval No. ChiCTR2100043796), registered 6 June 2021. The final revised draft and informed consent have been reviewed and approved by the Sichuan Regional Ethics Review Committee of The TCM/Medical Ethics Committee of The Affiliated Hospital of Chengdu University of TCM (No. 2020KL-065), registered 1 December 2020. If there is any amendment to the protocol, approval must be again sought from the Ethics Committee.

Recruitment

Participants will be recruited by doctors from the The Affiliated Hospital of Chengdu University of TCM, The Affiliated Hospital of North Sichuan Medical College, The Affiliated Hospital of Southwest Medical University, The guangyuan Hospital of TCM. Prior to the start of the study, participants will be provided detailed information about the clinical study, including the purpose, treatment measures, schedule, and possible risks and benefits. Only those who agree to sign the informed consent and voluntary participation in the trial will be included in the study. The recruitment plan is expected to take half a year to complete.

Sample size

Using two sample rates of unordered classified data to compare sample size estimation formulas: $n = \frac{(u\alpha + u\beta)^2 (1 + 1/k) P(1-P)}{(P1-P2)^2}$, Set the type I error probability $U\alpha$ and $U\beta$ as the U value corresponding to $\alpha\beta$, It can be obtained by looking up the table. $P1$ and $P2$ represent the efficacy of the experimental group and the control group, which are generally pre-experiments. If it is not a preliminary experiment, the effective values reported in similar research literature can be synthesized. According to related literature^[19], the effective rate of the treatment group ($P1$) is 92.5%; the effective rate of the control group ($P2$) is 80.00%, which is substituted into the formula $n1 = n2 \approx 130$, taking into account that the subjects may be uncooperative and halfway through the experiment Withdrawal, accidental death, etc., reduce the effective observation objects, so the number of cases is increased by 10% to ensure that the final available number of cases meets statistical expectations. Therefore, the total sample size is about 286 cases, and each group needs to observe 143 cases.

Randomization and assignment blinding

This study adopts a multi-center, random, and parallel control design. The random method is central block randomization without stratification factors, and each center competes for entry. The random sequence uses SAS statistical software to generate the experimental group and the control group at a ratio of 1:1.

Diagnostic criteria

Participants must meet the Western medicine standard of AIS diagnosis. Refer to the diagnostic criteria for cerebral infarction in the Chinese Medical Association "Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke" in the 2018 edition. ☐ Acute onset; ☐ Focal neurological deficits (weakness of one face or limb, numbness and language impairment, etc.), a few are general neurological deficits; ☐ Responsible lesions or symptoms/signs on imaging lasting more than 24 hours; ☐ Exclude non Vascular etiology; ☐ Cerebral CT/MRI excludes cerebral hemorrhage.

Qualification criteria

Inclusion criteria:

(1) Meet the diagnostic criteria of acute cerebral infarction.

(2) The onset time of ACI is less than 24 hours.

(3) The participants should be older than 18.

exclusion criteria:

(1) Patients in coma or patients with clinical manifestations of cerebral hernia, including the disappearance of the pupillary reflex on the same side and other manifestations of the third pair of cranial nerve palsy;

(2) Patients with pulmonary heart disease, unstable angina, or acute myocardial infarction within 6 months;

(3) The patient had neurological impairment before the onset of ACI (mRS>2);

(4) The patient is accompanied by severe cardiac insufficiency (NYHA heart function classification III-IV, see Appendix 2), severe liver failure (laboratory tests show that the liver function results exceed the upper limit of the normal range by more than 2 times, and severe renal insufficiency (Sera creatinine is more than 2 times the upper limit of the normal range), active gastrointestinal bleeding, or other diseases suggest that the survival time may be less than 6 months;

(5) The patient has participated in other clinical trials in the past 3 months;

(6) Patients who need emergency intervention for thrombus removal.

Termination and withdrawal criteria

During the research process, the patient can withdraw from the research at any time for any reason, or the researcher believes that the patient should suspend the research. For patients who are discontinued or lost to follow-up, the investigator should indicate the reason for withdrawal on the case report form (CRF), and the case that is lost to follow-up must notify the project monitoring team. Subjects should withdraw from the trial when the following situations occur: (1) The researchers believe that continuing the trial could be detrimental to the subjects. (2) The disease aggravation needs the endovascular therapy. (3) The subject refused to take the experimental drug as planned. (4) The subjects developed secondary cerebral infarction or cerebral hemorrhage during the course of treatment.

Test drugs

Formulation and packaging The test drug is Stroke Xingnaoye (provided by the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, 100ml/bottle), 25ml each time, once every 6 hours.

Treatment allocation Participants who meet the criteria for entry were randomly entered into the experimental group or the control group. The control group was the basic treatment with a placebo, and

the experimental group was treated with ZFXNY on the basis of the basic treatment. Medication method: The control group is the basic treatment. According to the patient's condition, it can reduce intracranial pressure, lower blood pressure, balance water and electrolytes, etc. Patients in the test group are added with the experimental drug Zhongfeng Xingnao fluid, which is taken one dose every 8 hours, 25 ML each time, for 30 days. The first administration time should be within 24 hours after the onset. Conscious patients were taken orally; patients with impaired consciousness were given by nasogastric tube. The placebo is composed of starch without any active ingredients. The color and taste of the placebo are the same as that of the TCM.

Intervention

Treatment plan

The trial consisted of a 30-day treatment phase followed by a 60-day follow-up phase. After 30 days of hospitalization, the subjects in both groups were given general treatment measures such as lowering intracranial pressure, controlling blood pressure, balancing water electrolyte and lowering temperature when necessary. The patients in the test group were given ZFXNY for stroke within 24 hours after onset, and the drug was given for 30 days. The participants were followed up 30 and 60 days after the cessation of treatment. Efficacy and safety were evaluated on the 30th, 60th and 90th day after treatment.

Outcomes

Primary outcome indicators: Modified Rankin Scale-Evaluate the percentage of subjects with no or only minimal dysfunction (mRS ≤ 2) at 30, 60 and 90 days after medication, and compare between groups. The mean mRS scores were compared between the two groups at 30 days, 60 days and 90 days after administration.

Secondary outcome indicators: ① NIH stroke Scale (NIHSS): The percentage of subjects whose neurological deficits were evaluated as normal or almost normal (ie NIHSS ≤ 1) at 30 days, 60 days, and 90 days after medication, were compared between groups. The percentages of subjects with normal or almost normal neurological deficit scores were compared between the two groups by light, medium and heavy ACI respectively. The mean NIH scores were compared between the two groups at 30 days, 60 days, and 90 days after medication (the 12th item of the remote motor function score in the NIH scale is not included in the total score). And according to the NIH score light, medium and heavy ACI stratified assessment. The percentage of subjects whose Glasgow score was equal to 5 was evaluated 30 days, 60 days, and 90 days after medication, and comparisons between groups were made. And according to the NIH score light, medium and heavy ACI stratified assessment. The mean scores of Glasgow results were compared between the two groups at 30 days, 60 days and 90 days after administration. And according to the NIH score light, medium and heavy ACI stratified assessment.

② Glasgow Coma Scale: The mean Glasgow coma scores were compared between the two groups at 30 days, 60 days and 90 days after administration. And according to the NIH score light, medium and heavy

ACI stratified assessment.

☒Barthel Index:The percentage of subjects who returned to normal (BI>95) was evaluated 90 days after medication, and comparisons between groups were made. And according to the NIH score light, medium and heavy ACI stratified assessment. The mean values of BI at 30 days, 60 days and 90 days after administration were compared between the two groups. And according to the NIH score light, medium and heavy ACI stratified assessment.

☒Case fatality rate: The fatality rate was evaluated 30 days after medication, and comparisons between groups were made.

Safety assessment

All participants who were selected for at least one treatment with the drug or the control group were assessed for safety (including adverse events, laboratory tests) . Adverse events and laboratory abnormalities will be used as indicators of safety evaluation.All adverse events during treatment will be tabulated according to the site and severity of the event. The incidence of adverse events and laboratory abnormalities are also listed.

Compliance

Before the patient is selected, the patient's allergy history and so on will be known in detail to ensure compliance.In addition, once a patient is enrolled in the trial, the researchers will keep a close eye on his or her physical condition and withdraw from the trial if it is not appropriate to continue.

Adverse events

The investigator should record all adverse events observed, obtained through non-inductive questioning, or reported by the subject, regardless of whether the adverse event is related to the trial drug, and should also record the new disease or the exacerbation of the existing disease during the study. For all adverse events, the investigator should judge the severity and follow up the subjects to clarify the outcome of the adverse event and determine whether it meets the criteria for serious adverse events.During the trial process until the last follow-up, if the subject has a serious adverse event, regardless of whether it is related to the drug, the investigator should report to the responsible unit within 24 hours of the event.In addition, serious adverse events will be reported to the steering committee and ethics committee within 24 hours.

Data management and quality control

Researchers participating in the trial are required to undergo relevant training in advance. The behavior of researchers must strictly abide by the trial requirements to ensure that they obtain true and reliable data. In accordance with the GCP principle, the researcher should keep all the detailed original documents of

the subjects. There should be trial process, medication status, laboratory inspection data, safety data and efficacy evaluation in the case report. The recorded data should be complete, timely and clear.

Statistical analyses

Before analyzing the data, we will check the completeness and accuracy of the data again. All the statistical tests involved in this study were bilateral tests, the significance level was $= 0.05$. The P value is reported as an exact value. All Statistical Analysis and reports are done using statistical software package SPSS 22.0 (Chicago, IL). The hypothesis tests of each parameter were compared between two treatment groups. We will use both the full analysis set (FAS) and the compliance plan set (PP) for statistical analysis. When the analysis conclusions of the above two data sets are consistent, the credibility of the test results could be enhanced. When inconsistent, the difference should be clearly discussed and explained.

Discussion

Acute cerebral infarction is a major public health problem worldwide. It's Characteried by high incidence, high disability, high mortality, unfavorable prognosis and high economic burden. In the recent years, certain breakthroughs have been made in endovascular interventional therapy. In the field of modern medicine, the current main treatment is still endovascular or drug therapy, but reperfusion injury and bleeding are the main adverse reactions of these treatments.[20,21] Thus, actively exploring safe and effective treatments is still a problem that medical scientists need to overcome. Traditional Chinese medicine is widely used in Asia and has fewer side effects, but there are few high-quality research results. The inclusion criteria of this trial excluded patients who could undergo early endovascular interventional therapy and thrombolysis. The results of this trial were limited to comparing the efficacy of traditional Chinese medicine combined with Western medicine and Western medicine alone. If this trail can verify the effectiveness and safety of traditional Chinese medicine treatment of acute cerebral infarction, we could further expand the application of traditional Chinese medicine treatment of acute cerebral infarction. The trail may be the basis for whether there is a another choice when doctors making the treatment decision on facing ACI.

Trail status

Recruitment started in July 2021 and is planned to end in January 2022, with 143 patients randomized. Treatment with finished in February 2022 We disposal the data at present. The current protocol version is 2.0, dated July 2021.

Abbreviations

ACI=Acute cerebral infarction, AIS=Acute ischemic stroke, TCM=traditional Chinese medicine

Declarations

Availability of data and materials: Not applicable.

Consent for publication Not applicable.

Competing Interest: The authors declare that they have no competing interests.

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Authors’ contributions The protocol manuscripts were finished by Wei Hu and Chenhui Zhang. Wei Hu and Chenhui Zhang contributed equally to this work and share first authorship. Chenhui Zhang and Hong Zhang conceived and designed the study.

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Figures

Figure 1

The illustration of he design for clinical studies is presented

Supplementary Files

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