

Measurement of cerebrovascular reserve by multimodal imaging for cerebral arterial occlusion or stenosis patients: protocol of a prospective, randomized, controlled clinical trial

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Study protocol

Keywords: stroke; cerebrovascular reactivity; cerebral blood flow; multimodal image; recurrence

Posted Date: December 10th, 2019

DOI: <https://doi.org/10.21203/rs.2.12484/v2>

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Version of Record: A version of this preprint was published on January 8th, 2020. See the published version at <https://doi.org/10.1186/s13063-019-3967-2>.

Abstract

Background Cerebrovascular reactivity (CVR), index of cerebral hemodynamics, might guide the treatment of ischemic stroke. However, the previous studies that the therapeutic strategy of stroke mainly depends on the degree of vascular stenosis with steady-state vascular parameters, such as cerebral blood flow, and CVR factors are not under consideration. Measurement of CVR by multimodal image might improve the prognosis for ischemic stroke.

Methods/design The study is a prospective, randomized, paralleled controlled clinical trial to examine the multimodal image evaluation for CVR. A total of 66 eligible patients will be recruited from Renji hospital, Shanghai Jiaotong University School of Medicine. The patients will be categorized based on CVR into two subgroups as follows: CVR>10% group and CVR<10% group. And the patients will be randomly assigned to medical management, percutaneous transluminal angioplasty and stenting, and intracranial and extra-cranial bypass groups in a 1:1:1 ratio. The primary end point is all adverse events and ipsilateral stroke recurrence at 6, 12, 24 months after the management. The secondary outcomes include the CVR, the National Institute of Health stroke scale and the Modified Rankin Scale at 6, 12, 24 months.

Discussion Measurement of cerebrovascular reserve by multimodal image is recommended by most recent studies to guide the treatment of ischemic stroke, and thus its efficacy and evaluation accuracy need to be established in randomized controlled settings. This prospective, randomized, paralleled controlled registry study, together with other ongoing studies, will present more evidence for optimal individualized accurate treatment of ischemic stroke.

1. Introduction

Stroke is the second most common cause of death and major cause of disability worldwide after ischemia heart disease, especially in developing countries [1]. Ischemic stroke occurs when a blood vessel supplying blood to the brain is obstructed, and it accounts for about 87% of all strokes. A remarkable risk of recurrent ischemic stroke was reported in patients with symptomatic major cerebral arterial occlusion or stenosis[2]. Therefore, an effective therapeutic approach for intracranial artery stenosis is urgently required.

The treatment of ischemic stroke has been investigated by a number of high-quality trials: The Japanese EC-IC bypass trial (JET2) study revealed that compared with the medical arm of the Japanese EC-IC bypass trial (JET) study including patients with cerebral blood flow (CBF) < 80% and cerebrovascular reactivity (CVR) < 10% as a historical control, the incidence of ipsilateral stroke recurrence was significantly lower in the JET2 study, demonstrating that EC-IC bypass surgery is unlikely to benefit patients with CBF > 80% or CVR > 10% [3]. Another recent trial, that is aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS), demonstrated the use of aggressive medical management rather than percutaneous transluminal angioplasty and stenting (PTAS) with the Wingspan system in high-risk patients with atherosclerotic intracranial arterial stenosis

[4]. AL Hasan conducted a trial for treating ischemic stroke, and showed 14.7% risk of stroke or death in the stenting group versus 5.8% in the medical group at 30 days, and 23% in the stenting group versus 15% in the medical group at a median follow-up of 32.4 months. However, the treatment strategy of intracranial arterial stenosis or occlusion mainly depends on the degree of vascular stenosis, with or without consideration of hemodynamic factors at the distal end-to-side anastomosis of a bypass graft and CVR factors, or steady-state vascular parameters, such as CBF and cerebral blood volume (CBV). Hence, we presented a study protocol for measurement of CVR using multimodal imaging data for cerebral arterial occlusion or stenosis patients.

The CVR is the ability of cerebral vessels to dilate or constrict in response to challenges or maneuvers[5, 6]. In addition, CVR is thought to be an important index of the brain's vascular health, and provides vascular reserve information that is complementary to steady-state vascular parameters, including CBF and CBV[7, 8]. There have been two main approaches to measuring CVR. One approach attempts direct CBF measurements of the brain tissue with flow sensitive imaging techniques such as positron-emission tomography (PET), nuclear medicine (NM) techniques, CT perfusion, or MR perfusion before and after a vasodilatory stimulus. The second approach involves transcranial Doppler (TCD) measurement of flow velocities (typically in the middle cerebral artery) distal to a lesion both before and after a vasodilatory stimulus, with the increase flow velocity considered a surrogate for CVR [9–12]. we intend to precisely evaluate the change of CVR before and after surgery or medicine treatments by multimodal image including MR, CT and SPECT, so that we can make strategies of individualized accurate diagnosis and treatment for the ischemic stroke[3, 13].

Due to lack of effective therapeutic approaches for intracranial arterial stenosis or occlusion, the present trial was registered in Chinese Clinical Trial Registry database, and approved by Center for Reproductive Medicine at Renji Hospital (Shanghai, China). The present trial was designed to determine whether multimodal imaging data can effectively enhance the treatment strategy for adult patients with intracranial arterial stenosis or occlusion.

2. Patients And Methods

2.1 Study design

This prospective, randomized, controlled clinical trial aimed to examine the efficacy of multimodal image data based on CVR to treat ischemic stroke. A total of 66 patients, who met the inclusion criteria, were admitted to Center for Reproductive Medicine at Renji Hospital, Shanghai Jiaotong University School of Medicine (Shanghai, China). The eligible patients were categorized based on CVR into two groups as follows: CVR>10% group and CVR<10% group. In addition, these two groups were randomly assigned to the groups of medical management, single angioplasty, PTAS, and IC-EC bypass in a 1:1:1 ratio.

2.2. Inclusion and exclusion criteria

The eligible patients were identified if they met the following criteria: 1. Clinical requirements: (1) Males and females who aged between 18 and 70 years old, (2) Independency in activity of daily living (modified Rankin scale score of 0–2) on admission or after resuscitation; 2. Radiological requirements: (1) Occlusion or severe stenosis in the main trunk of the middle cerebral artery (MCA) or the supraclinoid segment of the internal carotid artery, (2) CT and MRI: No large infarction and no contrast enhancement in the infarcted area; 3. Signing the written informed consent form.

Exclusion criteria were as follow: 1. No independency in activity of daily living (modified Rankin scale score of 3–5); 2. Occlusive lesions of cerebral arteries due to diseases other than atherosclerosis; 3. Malignant tumors or multi-organ dysfunction involving the heart, liver, kidney, or lung; 4. Myocardial infarction within the past 6 months; 5. Uncontrolled diabetes showing a serum fasting blood glucose level of > 300 mg/dL, or requires insulin; 6. Hypertension with a diastolic blood pressure of > 110 mmHg; 7. Artery-to-artery embolism; 8. Cardioembolism.

2.3 Ethical approval and consent to participate

The study protocol was approved by the Ethics Committee of Renji Hospital. Furthermore, the present trial was registered on Chinese Clinical Trial Registry (Registration No. ChiCTR-IOR-16009635). The trial was performed in accordance with the Declaration of Helsinki. All the participants signed the written informed consent form prior to start of study. The principal investigator explained the content of the research plan with the patient; included of if they agree to use of their data and asked for permission for the research team to share relevant data with people from the Universities taking part in the research or from regulatory authorities. The principal investigator will obtain informed consent or assent from potential trial participants or the patient legal representative[14]

2.4 Randomization and allocation concealment

In this trial, randomization sequence was generated by an independent insitution who was not involved in the determination of eligibility.

2.5 Treatment protocol

The eligible patients underwent multimodal imagine to measure CVR. Regional CBF was quantitatively measured more than 3 weeks after the last ischemic attacks using CTP or SPECT (123I-IMP). A study of a small number of patients with chronic arterial stenosis compared ASL perfusion with ACZ challenge with iodine 123 N-isopropyl-piodoamphetamine

(123I-IMP) SPECT, and the fixed concentration of CO₂ was provided by a gas delivery system using a pressure transmitter to control gas blender with prospective gas targeting algorithms. Subjects underwent SPECT/CTP scanning, and asked to breath normally for 10 min. The region of interest (ROI) was designated manually in the cerebral cortex in the territory of ipsilateral MCA at the level of the anterior horn of the lateral ventricle. ROIs were also placed in bilateral cerebellar hemispheres and in the contralateral MCA territory as reference. Regional CBF was expressed as relative values (%) to normal

control values of each institute obtained from volunteers free of cerebrovascular disease. CVR was calculated as follows: $CVR (\%) = [(CO_2 \text{ challenge CBF} - \text{rest CBF}) / \text{rest CBF}] \times 100$. All treatment procedures and specific operating protocols for the management of ischemic stroke in our trial were standardized based on current guidelines.

Surgical intervention was microsurgical end-to-side anastomosis of a superficial temporal artery branch to a cortical branch of the middle cerebral artery. If superficial temporal branch would be inappropriate, the occipital artery could be used. For participants in the surgical group, preoperative and postoperative antithrombotic treatments were carried out by a neurosurgeon. Patients in the PTAS group received stenting when alarm symptoms were relieved after MT treatment. Participants in the nonsurgical group continued to receive the antithrombotic treatment preferred by their physicians. Targets for controlling risk factor were 130/85 mm Hg for blood pressure, 100 mg/dL for low density lipoprotein, 150 mg/dL for triglyceride, and 7% for hemoglobin A1C.

2.5 Study endpoints

Each patient was followed-up for 2 years by a pair of a neurologist and a neurosurgeon in participating institute. Primary and secondary end points were defined as all adverse events and ipsilateral stroke recurrence at 6, 12, 24 months after management, respectively. Neurological findings, intracranial CT/MRI, and CBF/CVR measurements were examined and reported at the time of enrollment and 6 months, 1 year, and 2 years after enrollment. Evaluation of the cognitive function and angiography were carried out at the time of enrollment and 2 years after enrollment. The functional outcomes were measured using CVR, the National Institute of Health stroke scale (NIHSS), and the Modified Rankin Scale (MRS) at 6, 12, 24 months after the management.

2.6 Data collection

The baseline data were collected including the following variables: hypertension, smoking and diabetes, clinical presentation (i.e., initial ischemic stroke, on admission and before treatment); neurological functions (NIHSS and MRS), vascular stenosis, timing of management, treatment procedure, neurological conditions within 72 h after treatment, complications during hospitalization, follow-up, and presumed reasons of death. There is no storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies.

2.7 Follow-up

In this trial, CTP and SPECT were followed-up 6 months after treatment. All the patients were followed-up after management by a neurosurgeon using the telephone interview or in-person interview. The neurosurgeon was trained before the registry and was not involved in the treatment of ischemic stroke patients. In outcomes after 6, 12, and 24 months, the MRS of 0–2 denoted satisfactory outcome, and the score of 3–6 presented poor outcome.

Data verification was undertaken in 20% of all cases to assess the accuracy of data collection. The monthly audit, check of data quality, and statistical analysis were conducted by a third party who was in charge of notifying principal investigator and Institutional Review Board of Renji Hospital about any issues that arise. Any serious adverse events were reported to the Institutional Review Board of Renji Hospital. Recommendations were forwarded to the principal investigators for reviewing risks and benefits. The Institutional Review Board had access to the interim results and made the final decision to terminate the trial.

2.8 Sample size and data analysis

The number of patients included in the registry was equal to 60, and this trial involved 66 eligible ischemic stroke patients, in which about 10% of patients lost follow-up. Data were presented as mean \pm standard deviation (SD) for continuous variables, and as frequency for categorical variables. Significances between variables were analyzed using Chi-square test. Associations between clinical variables and outcomes were analyzed, and predictors of long-term outcome were identified using univariate and multivariate regression analyses. The difference was expressed as an odds ratio (OR, with 95% confidence interval [CI]), and $P < 0.05$ was considered statistically significant.

Discussion

Previous studies showed that medical management, PTAS, and IC-EC bypass can be applied for ischemic stroke patient, however, which treatment method is more beneficial has still remained elusive [4, 15]. The present trial was designed to indicate whether measurement of CVR using multimodal imaging is helpful to improve the treatment strategy for adult patients with intracranial arterial stenosis or occlusion.

Increased risk of stroke was found to be associated with hemodynamic failure, which can be assessed with measurement of CBF using (^{15}O -) H_2O PET [16]. This gold standard technique, however, has not been presented for routine clinical imaging. Standardized blood oxygen-level-dependent functional MRI+CO₂ is a noninvasive and potentially widely applicable method to assess whole-brain quantitative CVR. In addition, SPECT/CTP combined with CO₂ challenge enables scholars to measure CBF and CVR, representing the degree of hemodynamic failure [17, 18].

It has been previously demonstrated an association between CVR impairment and risk of stroke conserved across testing modality (TCD or nuclear medicine (NM) technique) as well as the nature of the vasodilatory stimulus (acetazolamide or variation in inspired CO₂ levels). TCD is relatively inexpensive and widely available, while it does not provide additional information about brain parenchyma and is technically impossible in some cases due to lack of acoustic windows. In the present study, we accurately evaluated CVR for ischemic stroke patients by multimodal imaging methods (MRI, CT or SPECT), and explored the recurrence of ischemic stroke after treatment, thus, we could develop a new method for accurate diagnosis and treatment of ischemic stroke [9, 19, 20]. Our approach possesses a number of novel features compared with other relevant trials. Firstly, CVR in the ischemic stroke patients was

evaluated by multimodal imaging methods because those are widely applicable to assess whole-brain quantitative CVR. Some researches reported that SPECT is further sensitive than PET in evaluation of CBF and cerebral perfusion, while its spatial resolution is negligible [21, 22]. The above-mentioned findings demonstrate that multimodal imaging techniques can accurately reflect changes in CVR. Secondly, the current study categorized the eligible patients into the groups of medical management, PTAS, and IC-EC bypass based on and the rates of CVR.

Finally, we recorded all the data related to the changes of CVR before and after treatment by multimodal imaging. The adverse events during follow-up period were also taken and divided into ipsilateral stroke recurrence and all adverse events. We consequently found that such data could be help to analyze the effects of relevant confounding factors.

Our trial also indicated whether CVR can effectively and safely help improve the outcome in patients with intracranial arterial stenosis or occlusion. With respect to great challenges in performing a clinical trial on ischemic stroke, the necessity to huge amount of data is inevitable.

Trial Status

This protocol is the first version 1, which approved on May 12, 2019. The trial was started on June 6, 2018. We hope to achieve our research objectives by September 2020.

Abbreviations

CVR: Cerebrovascular reserve *PTAS*: Percutaneous transluminal angioplasty and stenting

CBV: Cerebral blood volume *CTP*: Computed tomography perfusion

MRI: Magnetic resonance imaging *PET*: Positron emission tomography

SPECT: Single-photon emission computed tomography

MCA: Middle cerebral artery *ICA*: Internal cerebral artery

EC-IC: Extracranial-intracranial bypass

Declarations

Acknowledgements

The authors express their gratitude to all members of the Clinical Research Center of Renji Hospital for their significant contribution in this study

Funding

This study was funded by Shanghai Shen Kang Hospital Development Center Research Program (Grant Nos. 16CR2048B and 16CR2045B).

Availability of data and materials

Not applicable.

Authors' contributions

XZP, JK, LY, WJQ, PYH, JYC, and ZXH designed the study. XZP and JK drafted the manuscript. JYC and ZXH revised the manuscript. All authors agreed to publish this trial. The data analyzed during the current study are available from the corresponding author on reasonable requests.

Ethical approval and dissemination

The study protocol was approved by the Ethics Committee of Renji Hospital (2016–143K).

There is no anticipated harm and compensation for trial participation and the informed consent will be obtained from all patients enrolled in the study. All of the patients data will be uploaded to the Electronic Data Capture(China Clinical Trial Database); and published articles, or a lecture at the Neurosurgery Conference.

Conflict of interest

The authors declare that there is no conflict of interest.

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Figures

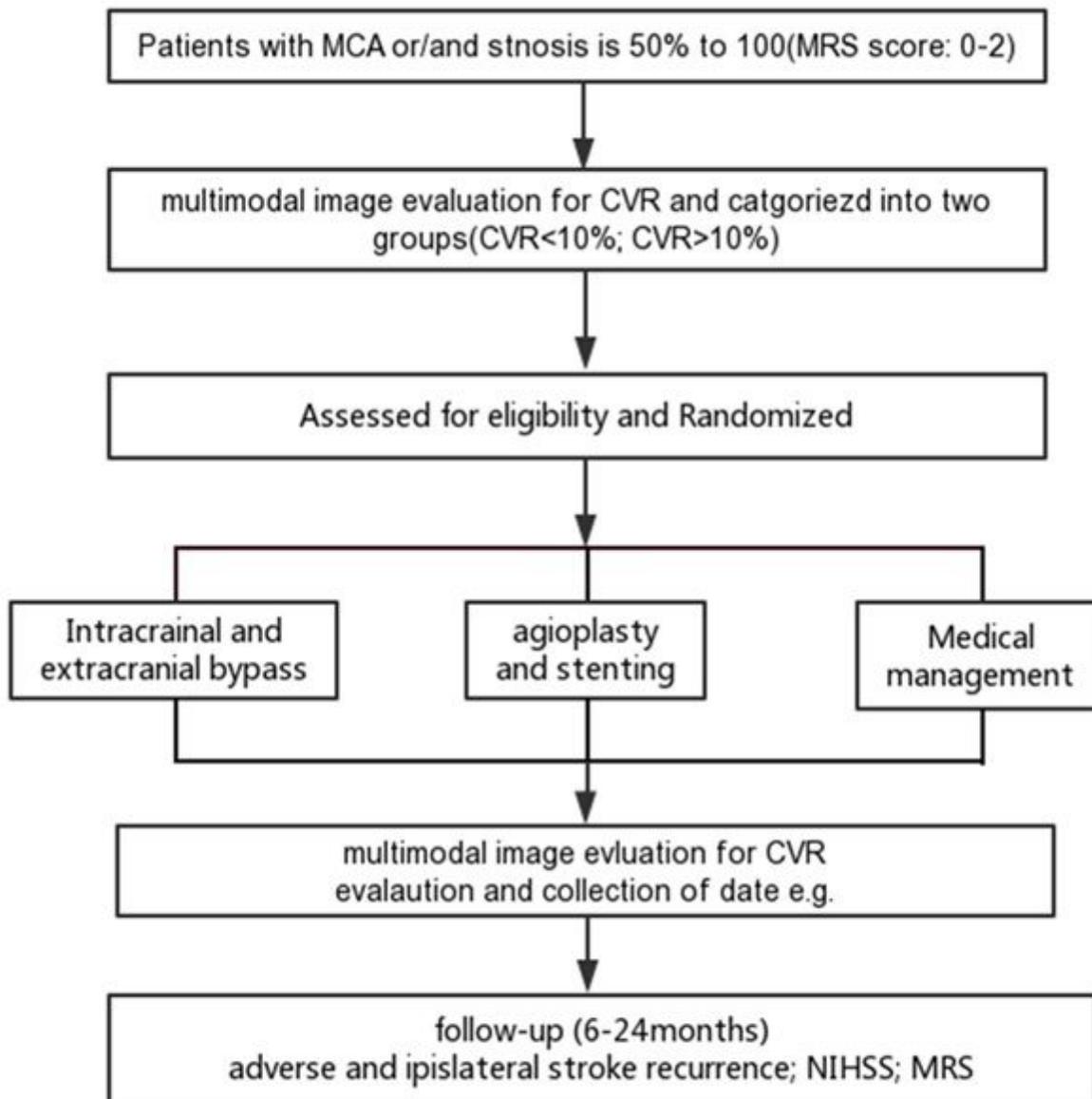


Figure 1

Study flowchart of our trial

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