Methylprednisolone in adjunctive to endovascular treatment for patients with acute ischemic strokes with established large infarct: A multicenter, randomized, double-blind, placebo-controlled trial (MIRACLE)

Informed Consent Form

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Sponsor： **The First Affiliated Hospital of Fujian Medical University**

Principal Investigators： **Wanjin Chen M D , P h D**

Dear participant,

You are invited to participate in a study conducted by Wanjin Chen (principal investigator) (13860501359) from the First Affiliated Hospital of Fujian Medical University. The title of the study is "Methylprednisolone in adjunctive to endovascular treatment for patients with acute ischemic strokes with established large infarct (MIRACLE): A multicenter, randomized, double-blind, placebo-controlled trial."

Your participation in this study is voluntary. This informed consent document provides information to help you decide whether or not to participate in this clinical research. This study has been reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University. The office phone number of the Ethics Committee is 0591-87981029. Your participation in this study will last for 3 months. If you agree to participate in this study, please read carefully and ask the researcher responsible for the study any questions you may have.

1. Research Objective:

Endovascular treatment has been beneficial for improving the prognosis of patients with acute ischemic stroke. However, post-procedure complications such as hemorrhagic transformation and malignant cerebral edema are significant contributors to patient mortality. Reducing these complications after endovascular treatment is crucial for ultimately decreasing the death rate among acute ischemic stroke patients. Glucocorticoids, widely used as potent anti-inflammatory and immunosuppressive agents, stabilize cell membranes, regulate intracellular and extracellular water and electrolyte balance, reduce cerebrospinal fluid production, and exert nonspecific antioxidant effects. They also prevent damage to cell membrane phospholipids by free radicals, actively regulate and restore blood circulation in damaged brain tissue, and alleviate cerebral edema. Methylprednisolone sodium succinate for injection, a moderately effective glucocorticoid, is widely used in clinical settings due to its minimal side effects and strong ability to penetrate the blood-brain barrier. A recent randomized controlled clinical trial (MARVEL) published in *JAMA* suggested that early combination therapy with methylprednisolone sodium succinate can reduce mortality and the incidence of symptomatic intracranial hemorrhage after endovascular treatment for acute ischemic stroke. However, this study excluded patients with large infarct core strokes (i.e., those with larger infarct sizes and an ASPECTS score <6 on imaging), who often exhibit more severe clinical symptoms and higher mortality and disability rates. Currently, there is insufficient evidence to support the safety and efficacy of early combination therapy with methylprednisolone sodium succinate for acute large core infarction recanalization. To address this gap, there is an urgent need to conduct research specifically targeting this patient population.

Therefore, we propose a multicenter, prospective, randomized, double-blind controlled trial design to investigate whether early combination therapy with methylprednisolone sodium succinate can improve clinical outcomes for patients with acute large core infarction, based on their revascularization status.

2. Research Process and Methods:

1) Before patients are enrolled in the study, doctors will inquire about and record their medical history and conduct routine examinations related to their condition. (Note: This study follows the diagnostic and treatment pathway for acute anterior circulation large vessel occlusion, and generally, no additional examination items will be added.) Once patients are qualified, they or their family members can voluntarily participate in the study and sign the informed consent form.
2) If patients or their family members voluntarily participate in the study, the following steps will be taken: Based on a random number generated by a computer APP, patients will be randomly assigned to the placebo

group (standard treatment) or the experimental group (methylprednisolone sodium succinate injection combined with the standard treatment) in a 1:1 ratio. There is a 50% chance for patients enrolled in this study to be assigned to each group. Both patients and doctors cannot know or choose any treatment method beforehand. ① For those in the placebo group (standard treatment), they will receive intravenous administration of a placebo while undergoing endovascular treatment. ② For those in the experimental group (methylprednisolone sodium succinate injection combined with the standard treatment), they will receive intravenous injections of methylprednisolone sodium succinate at 2mg/kg, once per day for three consecutive days, starting before the first surgery, along with endovascular treatment.

Patients will return to the hospital for a follow-up visit on the 90th day after enrollment to evaluate their mRS score, EQ-5D score, etc.

3) Other matters requiring cooperation from patients or their family members:

Patients need to bring their discharge summary, outpatient medical records, and relevant imaging data to the hospital for follow-up visits at the scheduled time agreed upon with the doctor (during the follow-up phase, doctors may contact patients via phone or in-person visits to understand their condition). Patient follow-up is crucial as professional cerebrovascular disease doctors will provide timely diagnosis and treatment advice based on the follow-up situation and formulate the next treatment plan.

If you agree to participate in this study, we will assign a number to each subject and establish a research file.

3. Possible Benefits of the Study:

If you agree to participate in this study and follow the prescribed medication and examination guidelines, there is a possibility that your condition may be alleviated, improving your survival time. However, we cannot guarantee this outcome, and it may not meet the expected results. Your study doctor will assess and observe your physical condition and medication use to ensure your safety as much as possible.

The information obtained from this study will contribute to understanding the efficacy and safety of methylprednisolone sodium succinate in treating patients with acute ischemic stroke. This information will benefit future patients.

4. Risks and Discomforts of the Study:

In this multi-center, randomized clinical trial studying the early combination therapy of methylprednisolone sodium succinate for acute large core infarction recanalization, potential risks include: ① elevated blood pressure, increased blood sugar, peptic ulcer, osteoporosis, and hypokalemia; ② neurological abnormalities manifesting as euphoria, excitement, anxiety, insomnia, and rarely, depression; ③ immunosuppression, which may easily induce or worsen infections. We will closely monitor your vital signs and ask you to inform us promptly of any discomfort, new changes in your condition, or any unexpected situations that may occur during the study, whether or not they are related to the research. We will assess these situations and provide appropriate medical treatment based on the specific circumstances to minimize risks. Additionally, we have purchased clinical research insurance for you, and the main body responsible for compensation is the Department of Neurology at the First Affiliated Hospital of Fujian Medical University.

During the study, patients are required to attend follow-up visits at the hospital on time for: ① neurological assessments such as mRS score and NIHSS score; ② blood tests including blood routine, blood biochemistry, and coagulation function; ③ imaging examinations like head CT/CTA/CTP and head MRI. These procedures will

occupy some time for the patients or their family members and may cause inconvenience or trouble.

5. Alternative Diagnostic and Treatment Methods:

If you do not participate in this study, you can choose other suitable treatment options. Please consult your doctor about your specific treatment plan. Your doctor will work with you to select the most appropriate treatment based on your condition.

6. Privacy Issues:

If you decide to participate in this study, your participation and personal information collected during the trial will remain confidential. All information related to you will be kept secret. Your samples will be identified by a study number rather than your name. Identifiable information about you will not be disclosed to members outside the research team unless you provide permission. All research team members and the study sponsor are required to maintain the confidentiality of your identity. Your records will be stored in the medical records department of the First Affiliated Hospital of Fujian Medical University and will only be accessible to researchers. To ensure that the study is conducted according to regulations, government authorities or members of the ethics review committee may, if necessary, access your personal information at the research site in accordance with the rules. When the results of this study are published, no personal information about you will be disclosed.

7. Costs:

The early combination therapy using methylprednisolone sodium succinate injection or conventional treatment for acute large core infarction recanalization is a commonly used clinical treatment for acute anterior circulation large vessel occlusion. The costs associated with the use of methylprednisolone sodium succinate injection or placebo for patients will be borne by the research team. All other diagnosis and treatment items will be charged according to clinical routine standards, and the expenses will be borne by the enrolled patients themselves.

8. Compensation:

If you suffer from any harm related to this clinical study due to your participation, you may receive free treatment and/or corresponding compensation. The expenses will be provided by this project.

9. Free Withdrawal:

As a subject, you can keep yourself informed about the information and research progress related to this study, and voluntarily decide whether to continue or withdraw from the study. After participating, regardless of whether any harm occurs, you can choose to notify the researcher at any time to withdraw from the study. Your data will not be included in the study results, and your medical treatment and rights will not be affected. During the trial, if it causes serious harm to you, the researcher will also suspend the study.

However, during the study, please provide true information about your medical history and current physical condition; inform the research doctor of any discomfort you experience during the study; do not take restricted medications, foods, etc.; and inform the research doctor if you have recently participated in other studies or are currently participating in other studies. If you fail to comply with the study plan, suffer from study-related injuries, or for any other reasons, the research physician may terminate your continued participation in this study.

10. Contact Information:

If you have any questions related to this study, or if you experience any discomfort or injury during the research process, or if you have any questions regarding the rights and interests of participants in this study, you can contact Dr. Wenlong Zhao at 13850172725.

11. Informed Consent Signature:

I have read this informed consent document, and my doctor (signature) has provided me with detailed explanations and clarifications regarding the purpose, content, risks, and benefits of this clinical trial. All of my inquiries have been answered, and I have a good understanding of this clinical study. I voluntarily agree to participate in this study.

Subject's signature: _____ Researcher Signature:_____

Contact Phone number: _____ Contact Phone number: _____

Date: _____/_____/____(YYYY/MM/DD) Date: _____/_____/____(YYYY/MM/DD)

(If the subject is illiterate, a witness signature is required. If the subject is incapacitated, consent from a legal representative is needed.)

Signature of Legal Representative/Witness: _____

Relationship with the Subject: _____

Date: _____/_____/____(YYYY/MM/DD)