MR Imaging Selection for Endovascular Treatment in Acute Ischemic Stroke at 6 to 24 hours: A Prospective Multicenter Randomized Clinical Trial of FVH-DWI Mismatch versus CT/MR Perfusion

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CLINICAL BACKGROUND AND PROBLEM

The efficacy and safety of endovascular thrombectomy (EVT) in patients with acute ischemic stroke (AIS) due to anterior circulation large-vessel occlusion (LVO) is well established in multiple randomized controlled trials (RCTs) in late treatment windows (6-16 hours)[2]. DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3) and DAWN (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo), relied on CT perfusion(CTP) or magnetic resonance diffusion and/or perfusion, and utilized automated imaging analysis with Rapid Processing of Perfusion and Diffusion (RAPID; iSchemaView, Menlo Park, CA) software to determine eligibility. Some centers triage patients solely based on MRI imaging, because the use of emergency CT/MR perfusion is limited in many treating centers.

It has been found that the fluid attenuation inversion recovery vascular hyperintensity (FVH) sign is an indicator of large vessel occlusion or stenosis, inadequate collateral circulation leading to slow blood flow and early ischaemia. The presence of the FVH sign is not only fairly consistent with areas of low perfusion, but its sensitivity and specificity is similar to that of time-flight magnetic resonance angiography (TOF-MRA) for the diagnosis of large vessel occlusion.

At the same time, the appearance and distribution range of the FVH sign in patients with acute macrovascular occlusion were closely correlated with the hypoperfused areas and their corresponding mean passage times and cerebral blood flow revealed by CT perfusion imaging. It was thus hypothesized that FVH could be an important and convenient imaging manifestation reflecting the underperfusion of brain tissue in patients with cerebral infarction with macrovascular occlusion.

In this study, a randomised controlled approach was adopted to assess the risk and prognosis of endovascular treatment by using the "FVH-DWI mismatch" to determine the presence of an ischemic penumbra and collateral circulation in patients, with the aim of establishing a simple evaluation method based on the indirect evaluation of collateral circulation on MRI to screen patients who underwent thrombolysis at 6 to 24 hours overtime. These data will be used to help evaluate if there is a consistency in thrombectomy

treatment effect related to MRI and CTP/MR perfusion imaging profiles.but is more easily replicable.

STUDY INTRODUCTION

1. **The sponsor of this study**

The sponsor of this research project:Tianjin Huanhu Hospital

This study is a multicenter study,The role of our institution in this study： **team leader unit**

The department and principal investigator(PI) of the project: **Neurosurgery,** PI：**Professor Ming Wei**

2**. Size of sample**

Total number of subjects planned to be included in this study：214

3. **Research Center**

The number of centers planned for this study： 5-10

4. **Research Objectives**

primary objective: Evaluation of the effectiveness of screening patients with large vessel occlusion in acute ischemic stroke at 6-24h with the use of nuclear magnetic plain scan prior to emergency endovascular treatment

Secondary objective: Evaluation of the value of "**FVH-DWI Mismatch**" in the emergency endovascular treatment of patients with large vessel occlusion in 6-24h acute ischemic stroke

5. **Study design**

5.1 **Study design**

The *MIEL* study is a multi-centre, prospective, randomized, open-label, blinded endpoint (PROBE) trial with a non-inferiority design. The study process was permitted by the ethics committee.

The study's emergency green channel team screened patients at 6-24 hours of onset for possible large vessel occlusion based on head CT scan and NIHSS score of ≥6 as the proposed cohort. Patients who met the entry criteria were then randomized 1:1 by the arriving stroke specialist into two groups 1 and 2 as follows, with the order of randomization being the responsibility of an independent investigator.

1.The MRI group performed DWI, FLAIRE, T1, T2 and MRA sequences.

2.The Control group underwent MRA or CTA, perfusion sequences, and F-stroke software (Brain Seal Smart Technology).

All patients were treated with standard Endovascular therapy and or optimal

drug therapy. The primary outcome was the overall distribution of modified Rankin scale scores at 90 days after surgery in the two groups of patients with modified intention-to-treat (**mITT**,defined as patients who had been optimally treated for acute macrovascular occlusion), as assessed by adjusted common odds ratios.Multiple secondary outcomes, including death, symptomatic intracranial hemorrhage, and ischemic regional reperfusion, were also assessed in the included study population.

5.2 Study population

5.21 Inclusion and exclusion criteria

General inclusion criteria:
1.Patients aged 18 years or older
2.Patients with acute anterior circulation ischemic stroke with an NIHSS score of ≥6 and RACE score ≥5 score at 6-24 hours of onset
3.No intracranial hemorrhage confirmed by cranial CT and CT ASPECTS score ≥ 6
4.Pre-onset Modified Rankin Scale (mRS) 0-2
5.Informed consent signed by all patients' legal representatives
6.Prognosis of survival 6 months or more.

Exclusion criteria:
1. Active hemorrhage or preexisting tendency to hemorrhage
2.CT shows hypointense areas exceeding 1/3 of the middle cerebral artery supply area, with significant midline structural displacement of cerebral edema
3.Rapid neurological improvement, NIHSS score less than 6, or evidence of spontaneous revascularization
4.Signs and symptoms typical of posterior circulation stroke, such as vertigo, nystagmus, choking, swallowing disorder, ataxia, and gaze to the affected side
5.A stroke attack with epilepsy that prevents an accurate NIHSS score from being obtained.
6.A platelet count of less than 100 x 10^9 /L
7.Hereditary or acquired bleeding tendency, coagulation factor deficiency, recent anticoagulant medication (INR>3 or PPT more than 3 times normal)
8.Presence of signs of cardiac, hepatic or renal failure
9.Baseline blood glucose <50mg/dL (2.78mmol) or >400mg/dL (22.20mmol)
10.Uncontrolled hypertension (SBP >185mmHg; DBP >110mmHg)
11.Expected survival less than 90 days.
12.Pregnancy.
13. Chronic obstructive pulmonary disease, inflammation of the lungs, pleural effusion, ARDS, irregular breathing and other pulmonary diseases requiring emergency treatment.
14.Patients with unstable vital signs (heart rate ≤ 50bpm or ≥ 120bpm, oxygen

saturation less than ≤ 90%. R ≥ 30bpm or ≤ 10bpm.
15.Patients who are unable to complete the 90-day follow-up
16.A history of severe allergy to contrast media
17.The presence of any other condition that is not suitable for endovascular treatment.

5.22 Subject Withdrawal from the Study

Although subjects are discouraged from withdrawing from the study, subjects may withdraw from the study at any time and for any reason without consequence. No consequences will be incurred, and further treatment will not be affected.

Subjects may withdraw from the study for the following reasons:

(1) Subject withdraws informed consent to participate in the study and refuses further follow-up

(2) Any clinical adverse event, laboratory test abnormality, or concurrent disease that, in the opinion of the investigator, is not in the best interest of the patient

(3) Other circumstances that, in the opinion of the investigator, warrant withdrawal from the study

(4) Loss to follow-up

(5) Death of the subject

(6) The investigator terminates the study

5.3 Study methodology

The study was designed as a randomized, double-blind, multicenter clinical trial.

5.31 Study groups

1.The MRI group performed DWI, FLAIRE, T1, T2, and MRA sequences.

2.The Control group performed perfusion sequences and processed them with F-Stroke stroke software (Brain Seal Smart Technology)

5.32 Blind method

Emergency department physicians were not aware of the experimental and grouping results.

The physician responsible for the assessment and the patient are aware of the grouping results; the attending physician is aware of the experimental and grouping results. Two neurointermediaries were assigned to the experiment. Two neurointerventionalists evaluate the procedure based on the readings provided by the respective group and decide whether to proceed.A third senior neurointerventional specialist decides.

The committee responsible for assessing primary and secondary outcomes and the imaging center specialists were not informed of the subgroup results. Outcome analysis was performed by an independent statistician, and results

were reported directly to the data and safety regulatory committee without the investigator being aware of the results at this time.

5.33 Study Implementation Process

Patient enrollment methods：

A） Emergency greenway triage based on signs and symptoms and NCCT: In this study, a team of emergency department neurologists screened patients for possible large vessel occlusion at 6-24 hours of onset based on head CT scan and NIHSS score ≥6 and RACE score ≥5 as proposed subjects.

B） Clearly diagnosed acute large vessel occlusion (ELVO)

Patients who have performed one of the MRI plain or perfusion examinations but do not meet the inclusion criteria for the DAWN or DEFUSE3 studies may be considered for inclusion. After enrollment, the appropriate imaging modality was selected according to the group as the basis for whether or not to perform interventional treatment.

Screening may be included in cases where either MRI or perfusion imaging is available at the time of the stroke specialist's evaluation of the patient, but the patient or authorized delegated family member is temporarily unable to decide whether to undergo the procedure, or under special irresistible conditions such as occupancy of the interventional suite.

Patients who met the entry criteria were then randomized 1:1 by the arriving stroke specialist into two groups 1 and 2 as follows, with the order of randomization being the responsibility of an independent investigator.

1.The MRI group performed DWI, FLAIRE, T1, T2 and MRA sequences.
2.The Control group underwent MRA or CTA, perfusion sequences, and F-stroke software (Brain Seal Smart Technology).

After randomization, the attending interventionalist decided the treatment based on the history and imaging data of the respective group. All patients were treated with the standard embolization procedure and or the optimal drug therapy. The primary outcome was the overall distribution of **mITT** patients' modified Rankin Scale scores at 90 days postoperatively in both groups, as assessed by the corrected co-ratio. Multiple secondary outcomes, including death, symptomatic intracranial hemorrhage, and

ischemic regional reperfusion, and safety outcomes were also assessed for the included study population.

5.34 Statistical methods

The primary efficacy analyses were performed by shift analysis, applying cumulative ordinal logistic regression to estimate the common OR and to evaluate the improvement in mRS scores in the **mITT** population. For secondary efficacy and safety analyses, statistical significance of differences between groups was assessed by Pearson χ^2 test or Fisher exact test for categorical variables, and by t test or Mann-Whitney test for continuous variables and safety endpoints for all patients. Descriptive analyses of adverse events were presented in the form of totals and events. Multivariate logistic or ordinal regression analyses were applied to determine independent estimators of good functional outcomes and were expressed as OR values and their 95% confidence intervals (95% CI). Two-sided values of $P<0.05$ were considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics for Windows, version 19 (IBM Corp).

5.35 Evaluation criteria for embolization procedures

MRI group: patient meets the criteria for entry; MRA meets the criteria for large vessel occlusion; and one of the following criteria is met: 1)presence of FVH-DWI mismatch sign (see Appendix) and infarct volume <70ml; 2) inability to obtain FLAIR sequence or to determine whether there is a FVH-DWI mismatch using the following criteria: patients ≥ 80 years old, preoperative NIHSS ≥ 6 points, DWI infarct volume < 21 ml, 2) patients < 80 years old, preoperative NIHSS ≥ 6 points, DWI infarct volume < 31 ml, 3) patients < 80 years old, preoperative NIHSS ≥ 6 points, DWI infarct volume < 31 ml 3) patients <80 years old with preoperative NIHSS ≥20 and DWI infarct volume less than 51 ml (see Appendix [9] for infarct volume evaluation methods); 3) patients with other conditions where MRI infarct volume cannot be determined, where MRI has failed, or where patients with atypical posterior circulation stroke are included are judged by operator experience as to whether to perform surgical treatment; Control group. Patients met the inclusion criteria; MRA/CTA was consistent with large vessel occlusion; preoperative NIHSS ≥6; F-Stroke (CBV <70mL; mismatch ratio ≥1.8; mismatch volume >15ml). CTA and CT perfusion were preferred in the Control group. The above results were evaluated by two neurointerventional specialists based on the readings provided by the respective groups, and the decision to perform the procedure was made by a third senior neurointerventional specialist in case of disagreement.

5.36 Quality monitoring of the treatment

There is no requirement for intravascular thrombectomy devices in this study, and devices that have been approved by the State Food and Drug

Administration of China devices approved by the State Food and Drug Administration of China can be used. Stenting is the preferred method in this study; if unsuccessful, suction devices may be used as a second-line option. The decision to use a combination thrombolytic strategy such as alteplase was left to the discretion of the treating physician based on the intraoperative situation, and the reasons for this were requested.

Control of surgical and pharmacologic bias: Patients undergoing an EVT procedure should have the first device (stent or aspiration catheter) used documented. The target time from imaging to decision grouping is less than 30 min; the target time from imaging to arterial pathway creation or puncture is less than 60 min; and the target time from imaging to revascularization is less than 120 min. Optimal treatment is given in the perioperative period or with drug therapy alone.

5.37 Outcomes

The primary outcome was the modified Rankin Scale score (mRS 90d) of a randomized group of modified intention-to-treat (mITT) patients (defined as patients with acute macrovascular occlusions treated optimally with endovascular or pharmacologic therapy) at 90 days (with an assessment time window of ±14 days) and analyzed for noninferiority. If the primary analysis indicated possible superiority, superiority was tested as a secondary objective. Data were collected by structured interviews (telephone interviews) with patients using a standardized form by trained physicians who were unaware of the subgroup results. A standardized written report of each interview was presented to two members of the outcome committee, who confirmed the scores and reached agreement.

The secondary outcomes were as follows：

Proportion of patients in each group receiving interventions Good prognosis for patients receiving interventions

1) Patient death within 90 days.

2)Successful reperfusion after embolization, defined as an extended Thrombolysis in Cerebral Infarction (eTICI) score of 2b, 2c or 3 at the time of the first intracranial angiogram.

3) Percentage of patients revascularized 24 to 72 hours after surgery (as determined by CTA).

4) NIHSS scores at 24 hours and 5 to 7 days postoperatively (or at discharge).

5)Final infarct volume (calculated by CBV or DWI) at 24 hours and 5 to 7 days postoperatively (or at discharge).

6) Comparison of modified Rankin scores at 90 days (0 or 1 vs. 2-6; 0-2 vs. 3-6; 0-3 vs. 4-6; 0-4 vs. 5 or 6; and 0-5 vs 6).

7) Quality of life assessment at 90 days: European Five Dimensions and Five Levels Scale (EQ-5D-5L) scores (range, -0.39 [worst] to 1.00 [best]); Barthel

Index scores at 90 days (range, 0 [severe disability] to 100 [no disability]).

Safety outcomes: included all hemorrhage and symptomatic intracranial hemorrhage (Judged by the Heidelberg Classification of Hemorrhage); intraoperative arterial puncture site pseudoaneurysm and inguinal hematoma, cerebral infarction in an additional vascular area at 5 to 7 days, and death within 90 days. The timing of clinical evaluation included at baseline, 24 hours after randomization, 5 to 7 days, or at discharge, whichever occurred first, and 90 days (with an assessment time window of ±14 days).

All clinical evaluators should receive on-site and web-based video training on how to perform clinical evaluations. Imaging results are evaluated in a separate imaging core laboratory by trained personnel who are unaware of the subgroup results. All images were reviewed by two individuals and disagreements were reached. We used F-Stroke software for the final automated analysis of infarct lesion volumes.

5.4 Specific Study Sessions

5.41 Signing the informed consent form

Patients should sign an informed consent form before enrollment, and the investigator should explain the content and significance of the study to patients and their families, and inform them of their rights and obligations. The informed consent should be signed by the patient and his or her legal representative.

5.42 Prior to randomization

The following data must be collected for all subjects prior to randomization and registration:

Confirmation that all enrolled patients meet the inclusion/exclusion criteria.

Demographic information and past history.

Vital signs.

Neurological function tests (NIHSS score, mRS score).

Routine blood count, blood biochemistry and coagulation.

Neuroimaging:MRI/CT to assess for intracranial hemorrhage; MRA/CTA/DSA to confirm that the occlusion occurred in a large vessel of the anterior circulation, such as the internal carotid artery (ICA) or the M1 segment of the middle cerebral artery.

Determination of time points: For consistency and clarity, a time standard was established for this study, namely time 0 "t = 0" defined as the time of randomization; that is, after CT exclusion of intracranial hemorrhage and suspicion of acute anterior great vessel occlusion (ICA or MCA-M1) based on clinical signs and symptoms, all subsequent time points (e.g., 24 hours, first day of the week, and second day of the week) were determined. All subsequent time points (e.g., 24 hours, days 5-7, 30, and 90) were used as a

reference for randomization time (t=0). Time recording format: X day, X month, X month, X hour, X minute.

5.43 Endovascular Treatment Specifications

Endovascular therapy includes mechanical embolization and balloon dilation or stenting. Thrombectomy allows the use of CFDA-approved thrombectomy devices such as stent-like devices and aspiration systems. For patients with underlying atherosclerotic stenosis after embolization, balloon dilation may be used alone, and stenting may be performed if necessary. For occluded vessels, no more than 5 thrombectomy attempts should be performed. Remedial measures after failed thrombectomy are permitted by pharmacologic arterial thrombolysis or intravenous infusion of antiplatelet agents, such as urokinase or rtPA arterial thrombolysis; rtPA is generally 1/3 of intravenous thrombolysis and can be administered intracatheterally, usually at a rate of 1 mg/min. urokinase is usually administered at a total dose of no more than 600,000 u at a rate of 1 to 20,000 U/min. Remedial therapy with balloon angioplasty or stenting is allowed. Failure to achieve a reperfusion grade of mTICI2b after remedial therapy is considered a failure of thrombus retrieval, and the case is considered a violation of the enrollment protocol, and the data can only be analyzed by mITT and cannot be included in the protocol compliance data set for PP analysis. In the case of re-occlusion at 24 hours after the procedure, it was also considered a recanalization failure and a violation of the enrollment protocol, and the data were analyzed only by mITT and not by PP.

Termination of endovascular therapy

1)Neurological deterioration suspected to be caused by intracranial hemorrhage;
2)Puncture time from the groin was up to 2 hours.
3)Spontaneous recanalization of the vessel.
4)The same site was embolized up to 5 times.For the procedure, the time of revascularization should be noted in detail;
5)the time from imaging to revascularization, the time from onset to revascularization, and the time from admission to revascularization should be calculated and used as baseline information for comparison between the 2 groups.

Type of surgical anesthesia

The surgery is performed by local or general anesthesia.

5.5 Postoperative management

5.5.1 Postoperative antiplatelet and anticoagulation therapy

According to the 2013 and 2018 AHA/ASA guidelines for the early management of acute ischemic stroke [7,8], antiplatelet therapy can be

continued for patients with intraoperative stents, while antiplatelet and anticoagulation therapy should not be initiated within 24 h for patients without intraoperative stents until intracranial hemorrhage has been ruled out by cranial imaging at 24 h postoperatively. Treatment. For non-atrial fibrillation patients, dual antiplatelet therapy (aspirin 100 mg + hydroclopidogrel 75 mg once daily; change to monotherapy after 90 days) and for atrial fibrillation patients, warfarin anticoagulation; the target dose of warfarin is to maintain INR: 2.0-3.0. In addition, newer anticoagulants are available as alternatives to warfarin, including dabigatranate; rivaroxaban; and apixaban. In addition, newer anticoagulants are available as alternatives to warfarin, including dabigatranate; rivaroxaban; and apixaban, selected on an individual basis and applied according to the drug's instructions.

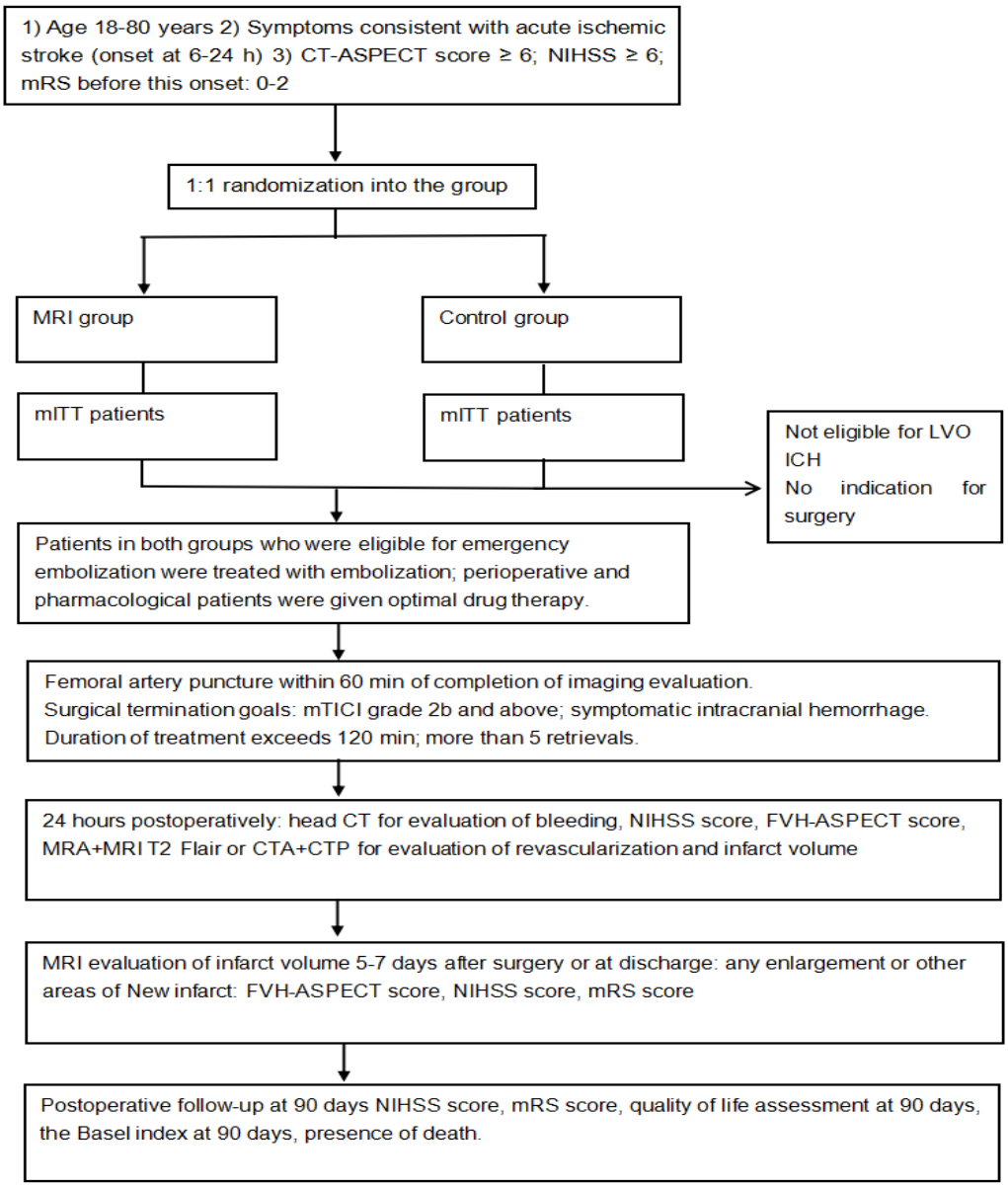
5.5.2 Blood pressure management

To prevent overperfusion syndrome, according to the 2013 and 2018 AHA/ASA guidelines for the early management of acute ischemic stroke [7,8], preoperative blood pressure should be controlled below 180/105 mm Hg (1 mm Hg = 0.133 kPa) in revascularized patients, and 20-30 mm Hg below basal blood pressure in hypertensive patients after revascularization, but not below 90/60 mm Hg. When the blood pressure fluctuates abnormally, we should be alert for complications such as intracranial hemorrhage or acute cardiac insufficiency. We recommend that the patient's blood pressure should be measured every 3-5 min during the procedure, and the blood pressure threshold should be sought for the individual patient based on a comprehensive assessment of the patient's cardiac function, vascular condition, and collateral circulation.

5.5.3 Blood glucose management

Evidence suggests that post-stroke hyperglycemia can affect stroke prognosis, so postoperative glucose should be controlled at 140-180 mg/dl (7.7-10 mmol/L) in accordance with the 2013 and 2018 US AHA/ASA guidelines for the early management of acute ischaemic stroke [7,8]; care should be taken to prevent and control hypoglycemia.

Flow chart of this study



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