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Acute Ischaemic Stroke Cooperation Group of Endovascular Treatment (ANGEL) registry: study protocol for a prospective, multicentre registry in China

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ABSTRACT

Background and purpose Endovascular treatment could improve functional outcomes and reduce mortality in patients with intracranial large artery occlusion. This registry aims to evaluate the endovascular treatment delivery and to improve endovascular treatment algorithm in clinical practice for patients with stroke in China.

Methods and analysis This multicentric, nationwide, prospective registry plans to include 20 stroke centres and recruit 900 consecutive AIS patients with large-artery occlusion under endovascular treatment. This registry will enrol acute large vessel occlusion patients suitable for endovascular treatment and the inclusion and exclusion criteria. In this study, 90 days functional independence (modified Rankin Scale score ≤2) is the primary efficacy endpoint. The procedural efficacy endpoint of this registry is target artery recanalisation defined by modified Thrombolysis in Cerebral Infarction score 2b or 3 after endovascular therapy. Symptomatic intracranial haemorrhage with 24±3 hours after the procedure is the primary safety endpoint of this registry.

Ethics and dissemination Beijing Tiantan Hospital's Ethics committee and all other participating centres approved the protocol and data collection of Acute Ischaemic Stroke Cooperation Group of Endovascular Treatment registry. Each participant or representative had a written informed consent.

INTRODUCTION

The results of positive trials for mechanical thrombectomy (MT) had brought a new era for large artery occlusion patients suitable for endovascular intervention treatment.[1–6] Studies had shown the benefits of MT in patients with acute intracranial large artery occlusion. In 2015, American Heart Association/American Stroke Association renewed the guidelines based on positive randomised controlled trial for acute ischaemic stroke patients' selection for endovascular treatment.[7] Endovascular procedures could provide significant clinical benefit for selected patients with large artery occlusion in anterior circulation. However, most of these trials were carried out in America, Europe and Australia, where the most common reason for acute large artery occlusion is cardiac embolism.[1–5 8–10]

In Asian population, the predominant reason for ischaemic stroke is intracranial atherosclerosis (ICAS) which is quite different from Caucasian population that have a high rate of extracranial large artery atherosclerosis. In Chinese population, ICAS is estimated to be from 33% to 50% of acute ischaemic stroke.[11] It is proved that MT could also benefit Chinese population with acute large vascular occlusion.[12 13] We should organise the systems of care to facilitate MT's delivery. The Acute Ischaemic Stroke Cooperation Group of Endovascular Treatment (ANGEL) registry was designed to evaluate the endovascular treatment delivery and to improve endovascular treatment algorithm in clinical practice in China.

METHOD/DESIGN

This multicentric, nationwide, prospective registry will include 20 comprehensive stroke centres in China, and consecutively recruit 900 AIS cases under endovascular treatment. For acute ischemic stroke (AIS) patient eligibility for inclusion, the legally authorised representative will be informed for the written informed consent of ANGEL registry before inclusion.

In all the patients, multiple indicators of will be evaluated at baseline, 24 hours, 7 days (or at the day of discharge) and 90 days (see online supplementary table 1) during the registry. Beijing Tiantan Hospital (China) sponsored and conducted this registry and also responsible for the analysis of data. The conduction, safety and efficacy of this registry

Box 1 Inclusion criteria for Acute Ischaemic Stroke Cooperation Group of Endovascular Treatment registry

Inclusion criteria

1. Age more than 18 years.
2. Clinical diagnosis of ischaemic stroke; the symptoms of stroke last for more than 30 min and has not significantly relieved before treatment.
3. Modified Rankin Score less than 2 before this stroke.
4. Onset to puncture time less than 12 hours for anterior circulation stroke and less than 24 hours for posterior circulation stroke.
5. CTA, MRA or DSA was performed when clinical symptoms severity suggested proximal vessel occlusion, including internal carotid artery, middle cerebral artery (MCA)M1/M2 segment, basilar artery occlusions or dominant vertebral artery occlusions (functional basilar occlusions).
6. Complete the informed consent form by patient or patient's legally authorised representative after receiving information about data collection.

Box 2 Exclusion criteria for Acute Ischaemic Stroke Cooperation Group of Endovascular Treatment registry

Exclusion criteria

1. Acute Stroke Prognosis Early CT score (ASPECTS) 0–6 by baseline non-contrast CT or diffusion-weighted image (DWI) (reveals a moderate/large core) in the territory of symptomatic intracranial occlusion or DWI lesion volume >70 mL for anterior circulation, or posterior circulation (pc-ASPECTS) 0–6, or Pons-midbrain index ≥3 for posterior circulation.
2. Seizure at the beginning of stroke.
3. Prior stroke within the last 3 months.
4. Pre-existing neurological or psychiatric disease which might confound the neurological and functional evaluations.
5. With less than 3 months life expectancy.
6. Previous clinical history of disease of intracranial haemorrhage, subarachnoid hemorrhage (SAH), arteriovenous malformation (AVM) or tumour.
7. Increased bleeding risk disease during the last 90 days.
8. In the past 10 days with the history of haemorrhagic disease, significant trauma or major surgery.
9. Uncompensated hypertension (systolic blood pressure more than 185 mm Hg or diastolic blood pressure more than 110 mm Hg with three repeated measures at least 10 min apart.
10. Renal failure (serum creatinine more than 2.0 or glomerular filtration rate less than 30).
11. Intravenous thrombolytic therapy with a dose of more than 0.9 mg/kg alteplase or 90 mg
12. Platelet count less than $50x10^3$/L.
13. Blood glucose less than 2.8 or more than 22.2 mmol/L.
14. Previous history of haemorrhagic diathesis, coagulation factor deficiency or under oral anticoagulant therapy with International Normalization Ratio (INR) >3.0.
15. Contraindications of digital subtraction angiography (DSA) examination.
16. Pregnancy.

is supervised by an independent data and safety monitoring board (DSMB).

STUDY STATUS

Recruitment of patients commenced in June 2015 and ended by December 2017.

PATIENT POPULATION

Any AIS patient suspected to be with large artery occlusion, suitable for endovascular therapy within onset to puncture (OTP) time <12 hours for anterior circulation stroke (ACS), OTP time <24 hours for posterior circulation stroke (PCS) and meeting the registry's enrolment criteria is eligible (boxes 1 and 2).

ENDOVASCULAR TREATMENT

Femoral artery puncture with local anaesthesia is the most common approach for the endovascular treatment. If needed, conscious sedation also could be used. If the patient is with the risk of airway compromise, the intubation is performed. When the patient is dysphoric and the conscious sedation is with a high risk, general anaesthesia will be induced. Blood pressure (BP) will be maintained below 180/105 mm Hg during the procedure. The use of heparinisation is disputed. Commonly, heparinisation is not suggested unless there is a high coagulation state or expected operation for a long time. Heparin saline is allowed for catheter flushing. DSA is quickly performed after femoral puncture (DSA is suggested to finish in 5–10 min for occluded artery and arteries necessary for collateral compensatory).

When available, commonly an 8 Fr balloon guiding catheter (BGC) is placed into the cervical internal carotid artery (ICA). If BGC is not available, a long sheath could be placed into the cervical ICA, or a 6–8 Fr guiding catheter could be slowly placed into the ICA. Distal access catheter could be used according to operator's will. A 0.014-in microwire will be used to guide the microcatheter to the distal part of occluded artery. The position of microcatheter should be confirmed by a gentle injection of contrast in the microcatheter and this also could exclude the perforation of artery. Saline is injected into the microcatheter to flush the contrast and a retrievable stent should be placed into the microcatheter. After delivery of the stent, a control angiography will be performed. The placement and the status of stent and artery could be confirmed. The device will be placed in the occluded artery for about 5 min. The BGC will be inflated and the stent will be smoothly pulled back with microcatheter together. A large syringe (20–50 mL) will be used for BGC or guiding catheter under manual aspiration to perform a flow reverse of occluded artery successful recanalisation is defined as modified Thrombolysis in Cerebral Infarction (mTICI) ≥2b in all treatable vessels.

Intra-arterial thrombolysis is allowed to be conducted in this registry at operator's will. Recombinent tissue plasminogen (rtPA) or urokinase (UK) is suggested if intra-arterial thrombolysis is considered. The best dose and rate is

not fixed and we suggest 1 mg/min alteplase for no more than 40 mg or intra-arterial (IA) 10–30 thousand unit/min urokinase for no more than 1 000 000 million unit. If the patients had received intravenous alteplase previously, intra-arterially dosage should be less than 30 mg alteplase or 400 000 U urokinase.

If the patient is suspected to be an atherosclerotic occlusion of the artery. In case of difficulty in passing the 0.21-inch microcatheter through the occlusion site, a 2 mm balloon is placed to perform angioplasty to facilitate the passing of microcatheter. After removal of the stent, if underlying stenosis of occluded artery is suspected, for to exclude vasospasm or dissection another angiogram is needed. Intracranial angioplasty and/or stenting for underlying ICAS are introduced by the determination of the operator. Rescue angioplasty or stenting is suitable for possible ICAS patients with stenosis degree >70% or stenosis with distal blood flow impairment or repeated occlusion of occluded artery after thrombectomy. If angioplasty or stenting is performed, additional low-dose bolus of tirofiban (0.25 mg-1 mg) followed by intravenous continuous infusion (0.1 µg/kg/min) for 12–24 hours are suggested as alternative rescue therapy. A cone beam CT is needed to exclude intracranial haemorrhage (ICH) if available. If not feasible, a plan CT should be performed. Afterwards, intravenous tirofiban was bridged with dual antiplatelet (100 mg aspirin and 75 mg clopidogrel once daily) and overlapped for 4 hours before tirofiban cessation if ICH was excluded by 24 hours post-MT CT. If tirofiban was not used, dual antiplatelet was given after 24 hours as conventional therapy. All operation and medication details were digitally documented for further analysis. After endovascular treatment, patients will be given standard medical therapy in intensive care unit and following the guideline.[14] BP should be controlled below 180/105 mm Hg during the whole procedure. An MRA or CTA will be further performed to evaluate the artery about 24 hours after the procedure.

PRIMARY ENDPOINT

In this registry, 90 days functional independence (modified Rankin Scale ≤2) is the primary efficacy endpoint. After the endovascular treatment, the final mTICI score of 2b–3 is the procedural efficacy endpoint of this registry. Symptomatic ICH (sICH) within 24±3 hours after treatment is the primary safety endpoint. sICH was defined according to European Cooperative Acute Stroke Study III (ECASS-III) and any ICH associated with clinical deterioration (increase ≥4 points in National Institute of Health Stroke Scale (NIHSS).[15]

SECONDARY ENDPOINTS

The secondary endpoints are correlated with the use of the endovascular treatment device and the procedure. Secondary endpoints for 24±3 hours postprocedure: cerebral infarction volume by CT scan, arterial reperfusion rate by, changes in NIHSS score; secondary endpoints for 14 days or at discharge: serious adverse events (SAEs), all-cause death, changes in NIHSS score; secondary end points for 90±7days: all-cause death, changes in NIHSS score, qualify of life European Quality of Life-5D (EQ-5D and Barthal Index (BI).

EXPLORATORY PURPOSE

The influence of different classification of The Trial of Org 10 172 in Acute Stroke Treatment on functional outcomes, arterial recanalisation, sICH and procedure duration of thrombectomy at 90 days. The influence of different gender on 90 days functional independence, arterial recanalisation, sICH and SAEs. The influence of different anaesthesia type on functional independence, arterial recanalisation, sICH and procedure time of thrombectomy at 90 days. The influence of antiplatelet drugs on 90 days functional independence, arterial recanalisation and sICH. The influence of anticoagulation drug on 90 days functional independence, arterial recanalisation and sICH. The influence of stenosis of occluded artery on 90 days functional independence, arterial recanalisation, sICH and procedure duration of endovascular treatment. The influence of baseline BP and glucose on primary results.

STATISTICAL ANALYSIS

Logistic regression model will be adopted for primary outcome between the subgroups analysis. During the analysis, factors that may cause potential confounding will be considered. We will also perform multivariable regressions adjusting for potential covariates and adjusting for the propensity score.

Similarly, logistic regression model will be used as well for secondary outcomes. Evaluation of the safety assessments, additional measurements during the trial (including treatment interruption/discontinuation, use of concomitant medications and lifestyle evaluation) will be based on appropriate summary statistics. For to determine the propensity for thrombectomy regardless of the outcome, this study will use non-parsimonious multivariable logistic regression model. To calculate the propensity score, all of the baseline characters are included in this study.

STRENGTHS AND LIMITATIONS OF THIS STUDY

The multicentre prospective registry was designed to evaluate the endovascular treatment delivery and to improve endovascular treatment algorithm in clinical practice for Chinese patients which possesses a high prevalence of ICAS. The safety and efficacy of endovascular treatment was evaluated. For ACS, the endovascular treatment will be performed within 12 hours from symptom onset and for PCS it should be within 24 hours. All the patients should in compliance with the inclusion and exclusion criteria. However, several limitations of the present study must be addressed. This registry focuses on the Chinese

population with high prevalence of ICAS and requires caution when generalising the findings to other ethnic groups.

DATA AND SAFETY MONITORING BOARD

This study has DSMB members which is independent of the researchers and the steering committee. DSMB is responsible for assuring that all subjects are not exposed to unnecessary risks and that the study is conducted in accordance with high scientific and ethical standard requirement. The DSMB has a responsibility for advising early termination of the study in the event of unexpected safety concerns or if treatment differences were apparent at the prespecified interim analyses.

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Contributors YiW, YoW and ZM designed the registry; XH and MY wrote the manuscript; NM, DM and FG revised the manuscript; ANGEL investigators participated in revising the protocol and collected the data.

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Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

Ethics approval This registry has been approved by the Centralized Ethics Committees of Beijing Tiantan Hospital and all other participating centers (see online supplementary table 2).

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