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Safety and efficacy of tirofiban in preventing neurological deterioration in acute ischemic stroke (TREND): Protocol for an investigator-initiated, multicenter, prospective, randomized, open-label, masked endpoint trial

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Abstract:

INTRODUCTION: Antithrombotic therapy prevents adverse ischemic events following acute ischemic stroke (AIS). Intravenous tirofiban provides desirable antiplatelet effects, especially in patients who are vulnerable to neurological deterioration (ND).

AIM: The aim of the study was to test the hypothesis that intravenous administration of tirofiban, initiated within 24 h of ictus and continued for consecutive 72 h, would be more effective than aspirin in reducing the risk of ND within 72 h of enrollment among patients with potentially atherothrombotic ischemic stroke.

METHODS: The Safety and Efficacy of Tirofiban in Preventing Neurological Deterioration in Acute Ischemic Stroke (TREND) trial is an investigator-initiated, multicenter, prospective, randomized, open-label, masked endpoint study. Its eligibility criteria included AIS secondary to potential atherosclerosis, a National Institutes of Health Stroke Scale (NIHSS) score ranging from 4 to 20 points, ineligibility for recanalization therapy, and administration within 24 h postsymptom onset. Randomization was performed at a 1:1 ratio to allocate 420 patients into two groups to receive an intravenous tirofiban bridge to oral antiplatelet drugs or direct oral antiplatelet drugs.

OUTCOMES: The primary outcome is the proportion of patients with a ≥4-point increase in NIHSS score within 72 h of intervention compared to the score at enrollment. The key secondary outcomes include changes in NIHSS score, modified Rankin scale (mRS) score at 90 days, and dichotomized mRS scores (0–2 vs. 3–6 and 0–1 vs. 2–6) at 90 days. The safety variables are symptomatic intracerebral hemorrhage, any intracerebral hemorrhage, and systemic hemorrhage within 72 h after randomization and 90-day mortality.

CONCLUSIONS: The TREND trial may identify the suitability of intravenous tirofiban as a routine clinical strategy to prevent ND in patients with AIS within 24 h of the onset of symptoms.

TRIAL REGISTRATION: http://www.clinicaltrials.gov (identifier: NCT04491695).

Keywords:

Acute ischemic stroke, antiplatelet therapy, neurological deterioration, tirofiban

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Introduction and Rationale

Neurological deterioration (ND), with an incidence of approximately 5%–40%, is common in patients with acute ischemic stroke (AIS).[1,2] Previous studies demonstrated that ND is strongly associated with a poor clinical outcome in patients with AIS, with mortality rates of 19% at discharge and 33% at 3 months.[3-5] Intracranial atherosclerotic disease is more prevalent in Asian countries such as China than in Western countries, and approximately half of Chinese patients with AIS have intracranial artery stenosis,[6] among whom early ND is more common than in patients with cardioembolism.[7,8] Thrombosis progression is the primary underlying pathophysiological process of ND.[9] Antithrombotic therapy is essential for preventing adverse ischemic events after AIS and effectively prevents ND caused by stroke progression secondary to thrombosis progression in patients with minor AIS.[10,11] Currently, despite the recommendation to administer aspirin to patients with the National Institutes of Health Stroke Scale (NIHSS) scores of at least 4, the high resistance rates, along with the slow effects of oral drugs and swallowing difficulties in stroke patients, have increased the risk of ischemic stroke progression.[12-14] However, effective antiplatelet therapy regimen to prevent early ND remains unclear.

Tirofiban, a rapid-onset and nonpeptide-selective inhibitor of the platelet glycoprotein IIb/IIIa receptor, can prevent thrombus formation by inhibiting a common pathway for platelet aggregation.[15] In patients with acute coronary artery disease, tirofiban has been widely used and demonstrated to reduce the incidence of vascular complications and the requirement for revascularization if used early.[16,17] Several clinical studies have suggested the efficacy of tirofiban in AIS patients who were or were not treated with intravenous thrombolysis.[18-21] More recently, a large clinical trial demonstrated that treatment with tirofiban is more likely to achieve favorable outcomes in patients with recent onset of ischemic stroke or worsening neurological deficits and nonoccluded large- and medium-sized cerebral arteries.[22]

The Safety and Efficacy of Tirofiban in Preventing Neurological Deterioration in Acute Ischemic Stroke (TREND) trial is mainly aimed at determining whether the intravenous tirofiban, which starts within 24 h and lasts for 72 h, could effectively reduce early ND in patients with potential atherosclerotic AIS within 24 h of onset without an increasing risk of symptomatic intracranial hemorrhage (sICH).

Methods

Trial design

The TREND trial was an investigator-initiated, multicenter, prospective, randomized, open-label, masked endpoint trial, which complies with the principles of the Declaration of Helsinki. The trial scheme is illustrated in Figure 1. The trial was planned to complete enrollment in 3 years; participants were recruited from 10 comprehensive stroke centers in China.

Participant population

The inclusion criteria were as follows: age, 18–80 years; the presence of neurological deficits attributed to focal cerebral ischemia and an NIHSS score ≥4 but ≤20; within 24 h of symptom onset or time last known well and randomizable within 24 h of symptom onset or time last known well; the presence of paralyzed limbs that can actively move muscles (standardized motor examination rating scale score ≥2); and informed consent provided by the participants or their acceptable surrogates.

The exclusion criteria were as follows: AIS patients undergoing intravenous thrombolysis or endovascular thrombectomy; AIS caused by a determined or suspected cardioembolism as evaluated by trained local investigators; AIS of other causes, such as arteritis, moyamoya disease, or artery dissection; prestroke modified Rankin scale (mRS) score ≥2 or dyskinesia of the paralyzed limbs before the stroke; pregnant or lactating upon admission; known hematochezia, gastrointestinal bleeding, or other bleeding contraindicating antiplatelet therapy; allergic to tirofiban or its solvents; severe disease such as malignant tumor, liver cirrhosis, kidney failure, or congestive heart failure; gastrointestinal or genitourinary tract bleeding within 1 year of AIS; coagulation disorder, platelet dysfunction, or platelet count $<100 \times 10^9$/L; having undergone a major surgical operation or experienced severe trauma within 1 month of developing AIS; hemorrhagic retinopathy; chronic hemodialysis; presence of uncontrolled hypertension defined as a systolic blood pressure >180 mmHg or a diastolic blood pressure >110 mmHg; acute pericarditis; unavailability of follow-up data; coexistence of other neurological conditions complicating the outcome assessment during follow-up; ongoing treatment in other investigational therapy studies or lack of completed follow-up to the primary endpoints; with recurrent AIS and previously enrolled in the TRENT study; and any other parameters as determined by the investigators.

Randomization and masking

Participants were randomly allocated to the tirofiban and oral antiplatelet groups in a 1:1 ratio. Randomization was performed using a real-time web-based APP or WeChat application on a mobile phone or computer (https://iwrs.xhedc.com/) after their status was confirmed. Randomization was stratified by age (18–40, 41–60, and 61–80 years), occlusion site (anterior or posterior), and prestroke antiplatelet drug treatment. The participants were informed of the study medications, and the investigators

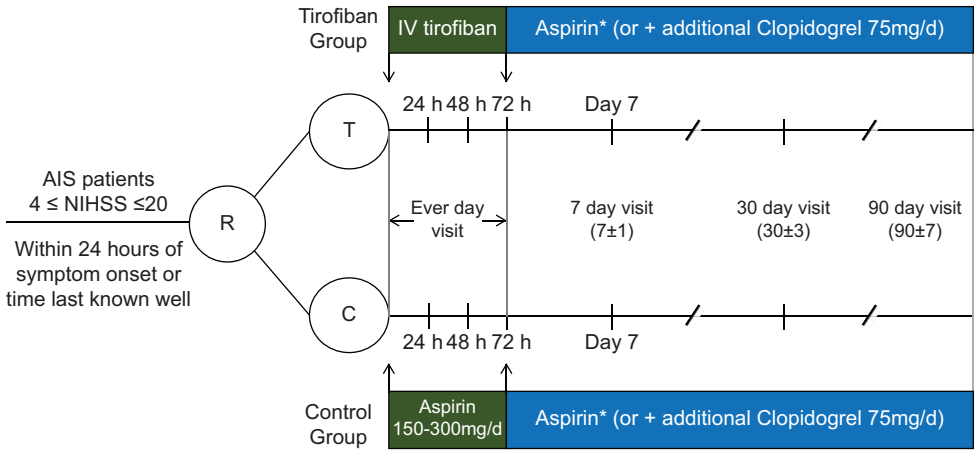

Figure 1: Trial design and treatment flow diagram. AIS: Acute ischemic stroke; IV: Intravenous; NIHSS: National Institutes of Health Stroke Scale. *Oral aspirin 150-300 mg per day for the first two weeks after symptom onset followed by 100-300 mg per day.

who performed follow-up evaluations of neurological function and examinations were blinded to the treatment allocation assignment and not be involved in caring for them. To ensure effective maintenance of blinding, medical records were not be accessible to the assessors. Regular monitoring was established to oversee the blinding process.

Treatments

In this trial, participants were randomly assigned to the tirofiban or oral antiplatelet group. All treating physicians tended to screen and manage risk factors according to the standard recommendations of international and Chinese AIS management guidelines.[12,23,24]

Regarding the antiplatelet therapy regimen, the tirofiban group received the following treatment: D1 to D3, intravenous loading dose tirofiban 0.4 μg/kg/min × 30 min, succeeded by a 0.1 μg/kg/min infusion for 71.5 h; and D4 to D90, aspirin 150–300 mg per day for the first 2 weeks after symptom onset, followed by 100–300 mg per day. The dose of aspirin was determined by the treating physician. When bridging to oral antiplatelet therapy, oral aspirin and intravenous tirofiban overlapped for at least 4 h, and intravenous tirofiban was discontinued. A loading dose of aspirin was strongly recommended if the patient did not receive oral aspirin before its administration.

The oral antiplatelet group received aspirin 150–300 mg per day for the first 2 weeks after symptom onset followed by 100–300 mg per day. The dose of aspirin was determined by the treating physician according to the patients' conditions.

In both groups of patients requiring monoantiplatelet therapy, aspirin was administered as the first choice. However, clopidogrel can be used as a substitute for antiplatelet drugs for patients who are unable to take aspirin. For participants requiring dual antiplatelet therapy after the first 72 h of randomization (i.e., ischemic stroke attributed to an intracranial large artery atherosclerotic stenosis of 70%–99%), aspirin in combination with clopidogrel (75 mg daily after an initial loading dose of 300 mg) was recommended. For any antiplatelet drug, a loading dose was recommended if the patient did not take it before the stroke.

Efficacy outcomes

The primary outcome of this trial was set as the proportion of ND within 72 h of enrollment, and ND was defined as a ≥4 points deterioration in the NIHSS score compared to the NIHSS score at enrollment.

The secondary outcomes included a reduction of ND as assessed by the NIHSS score, defined as an increase in NIHSS score by at least 2 points; the mRS score at 90 days; the proportion of participants who achieve nondisability, defined as an mRS score of 0-1 at 90 days or a return to a premorbid mRS score >1; the proportion of functional independence,defined as an mRS score of 0-2 at 90 days; and the change in NIHSS from baseline to 24 h, 72 h, and 7 days.

Safety outcomes

The primary safety outcome was the incidence of sICH assessed within 72 h based on the criteria of the European Cooperative Acute Stroke Study III.[25] Other safety outcomes included all-cause mortality within 90 days and the incidence of any intracerebral hemorrhage within 72 h after randomization, serious adverse events, and any adverse events.

Sample size estimates

This trial estimated the original sample size based on the primary efficacy outcomes. According to previous studies, the incidence of ND in patients within 24 h of onset was 20.0% within 72 h.[26-28] We expected a 10.0%

absolute difference in the proportion of patients when compared to between the intravenous tirofiban and oral antiplatelet groups. To demonstrate the expected treatment effect of a 10% absolute difference (50% decrease in relative term) with a type I error alpha of 0.05 (two sided) and a power (1−β) of 80%, a sample size of n = 400 participants (n = 200 each group) was required if participants were allocated in a 1:1 ratio. The final sample size was increased to 420 (n = 210 per treatment group) to compensate for possible dilution of the treatment effect because of loss to follow-up, revocation of consent, and participants who were randomly assigned but did not receive their assigned treatment due to the worsening of the condition. This estimation was performed using PASS version 11 (NCSS LLC, Kaysville, UT, USA; www.ncss.com).

Statistical analyses

The primary efficacy outcome was subject to both intention-to-treat and per-protocol analysis. Standard statistical principles were used for secondary and tertiary outcome analysis to compare parametric and nonparametric distributions as needed. Safety endpoints such as the proportion of patients experiencing sICH and 90-day all-cause mortality were compared by binary logistic regression analysis.

Data and safety monitoring board

An External Data and Safety Monitoring Board (DSMB) supervised data safety. The DSMB, consisting of three stroke neurologists and a statistician who are not involved in the study or affiliated with the sponsor, did the review of adverse events occurrence as its primary task and made recommendations to the executive committee regarding study safety. If there is a significant increase in the risk of adverse events in the tirofiban group compared to the control group, the trial will be stopped. The statistician prepared open and closed reports, and the DSMB convened roughly every 6 months. Additional meetings were scheduled when necessary. Reports pertaining to safety events were submitted to the DSMB by a statistician at the intervals determined by the DSMB.

Trial status

Recruitment for the TREND trial commenced on September 12, 2020. On December 21, 2022, all participants were randomized.

Discussion

As TREND is a trial of antiplatelet therapy for AIS, selection of the target population and initiation of therapy are important. Considering the high incidence of hemorrhagic transformation and potential neutral efficacy, stroke patients with cardioembolisms will be excluded.[29] The diagnosis of cardioembolic stroke is based on the etiology classification criteria of TOAST.[30] However, treatment initiated promptly is crucial for patients within 24 h of stroke ictus. Comprehensive examinations such as vascular evaluation and right heart contrast echocardiography may not always be fully executed in a limited timeframe. Therefore, suspected cardioembolism cases, according to the form of onset, head imaging characteristics, and other factors, were also excluded. In addition, patients with NIHSS scores out of the range from 4 to 20 are excluded from the study, as patients with NIHSS scores of ≤3 have been identified to benefit from dual antiplatelet therapy, whereas NIHSS scores >20 typically indicated poor conditions and a high likelihood of requiring thrombectomy treatment. In short, in this trial, patients with potential atherosclerotic stroke mainly secondary to platelet aggregation thrombosis and not receiving recanalization therapies will be recruited and treated within 24 h of stroke onset. What should be noted is that we also include younger adults suffering from AIS as the significant role of atherosclerosis in the younger Chinese population has been demonstrated.[31,32]

ND implies clinical worsening that may be stopped or prevented if accurately predicted and treated timely. However, internationally recognized definitions of ND in patients with AIS remain lacking. A previous study reported that >70% of ND cases occur within 72 h of stroke onset[9] and a change of 4-point NIHSS score is generally considered clinically significant in stroke patients.[33] Therefore, the TREND trial adopted the definition of ND as an increase of at least 4 points in the NIHSS score and the treatment time of intravenous tirofiban 72 h after stroke onset, which can not only cover the time window of a high incidence of ND but also avoid increasing the risk of hemorrhage transformation resulting from the long administration period.

Although intravenous tirofiban has been widely used in patients suffering from coronary artery disease, several trials have demonstrated its safety and efficacy in AIS patients who have not undergone reperfusion therapy. In previous studies on AIS, intravenous tirofiban was often administrated in accordance with the PRISM-PLUS protocol (0.4 μg/kg/min for 30 min followed by 0.1 μg/kg/min), and the results confirmed the protocol as relatively safe in patients with AIS despite the slightly increased risk of the incidence of sICH.[18-20,22] Therefore, the TREND trial will adopt intravenous tirofiban administration in accordance with the PRISM-PLUS protocol. Furthermore, with the significant risk of ND within 72 h of stroke onset, the choice to administer tirofiban consecutively for 72 h seems intuitive to cover the time window of high incidence of ND.

The study has several limitations. First, the results may not be generalized to patients with cardioembolic stroke, as they were excluded from the study. Second, as the trial was conducted in China, where atherosclerotic disease is prevalent, the results may not be perfectly applicable to other global populations. In addition, this study was unable to determine the safety and efficacy of intravenous tirofiban for patients with AIS and NIHSS scores outside the range of 4–20. Moreover, previous studies have shown that if an increase of ≥4 points in the NIHSS score is defined as ND, the pooled overall incidence of ND within 72 h of symptom onset ranged from 6% to 34%.[34-36] The estimation of this sample size based on parameters may have bias.

Summary and Conclusions

The results of the TREND trial will demonstrate whether intravenous tirofiban is safe and effective at reducing ND if it is initiated within 24 h of stroke onset and administered for a consecutive 72 h duration in patients with potentially atherothrombotic stroke. This trial will provide parameters for future studies that investigate the effects of antiplatelet therapy in patients with AIS. The findings of this trial are expected to have clinical implications in preventing ND during the acute phase of AIS, which may contribute to enhancing patients' adherence to treatment and improve the often strained relationship between patients and their health-care providers.

Author contributions

All the authors were responsible for the conception and design of the study. Jing Wang, Wenbo Zhao, Xunming Ji, and Qingfeng Ma revised and commented the draft and all authors read and approved the final version of the manuscript.

Ethical approval

This study protocol was reviewed and approved by the ethics committee of Xuanwu Hospital, Capital Medical University (No. 2019-093, dated on November 4, 2019) and each participating center.

Informed consent

Written informed consent will be obtained from all participants before randomization.

Data availability statement

Data sharing not applicable to this article as no datasets were generated and/or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

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