Safety and Preliminary Efficacy of Early Tirofiban Treatment After Alteplase in Acute Ischemic Stroke Patients

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Background and Purpose—We investigated whether early initiation of tirofiban, a glycoprotein IIb/IIIa antagonist, is safe, can reduce the risk of reocclusion, and improve outcomes in acute ischemic stroke patients after alteplase.

Methods—Forty-one patients received alteplase followed by intravenous tirofiban infusion for at least 24 hours. The incidence of symptomatic intracranial hemorrhage, systematic bleedings, and death was recorded. The National Institutes of Health stroke scale score was evaluated at 24 hours and at day 7 (or discharge). Modified Rankin scale was assessed at 3 months. Outcomes for these patients were compared with a propensity score–matched historical cohort with alteplase only.

Results—The incidence of symptomatic intracranial hemorrhage, death, or systematic bleedings (P=1.00) was not increased in the alteplase/tirofiban group. At 24 hours, fewer patients experienced reocclusion in the alteplase/tirofiban group (2.4% versus 22.0%; P=0.025). At day 7 or discharge, the median National Institutes of Health stroke scale score was significantly lower in the alteplase/tirofiban group (1 versus 6; P=0.002). At 3 months, more patients had favorable outcomes of modified Rankin scale 0 to 1 (70.7% versus 46.2%; P=0.026).

Conclusions—Intravenous tirofiban immediately after alteplase seems to be safe and potentially more effective when compared with alteplase alone for selected stroke patients.

Clinical Trial Registration—URL: http://www.chictr.org.cn/. Unique identifier: ChiCTR-TRC-14004630.

Key Words: acute ischemic stroke ■ outcomes research ■ safety ■ tirofiban ■ tissue-type plasminogen activator

The overall rate of recanalization induced by intravenous tissue plasminogen activator is only ≈46%, reocclusion occurs in 14% to 34% of the recanalized patients. This reocclusion is primarily attributed to the activation of platelets secondary to the local thrombus and endothelial injury.1,2

The ARTIS trial (Antiplatelet Therapy in Combination With rt-PA Thrombolysis in Ischemic Stroke) showed that using intravenous aspirin immediately after alteplase did not improve outcomes at 3 months. Instead, it increased the risk of symptomatic intracranial hemorrhage (sICH).3 However, considering the long-lasting and nonselective inhibitory effect of aspirin on platelets, the results of the ARTIS study do not completely eliminate the possible benefit of early antiplatelet therapy. The binding of the platelet glycoprotein IIb/IIIa receptor to fibrinogen is the final pathway leading to platelet aggregation and thrombus formation. Tirofiban, a selective nonpeptide glycoprotein IIb/IIIa antagonist, has a short half-life (=1.6 hour), and its prolonged bleeding time can be normalized within 4 hours after discontinuation.4 The safety of tirofiban was confirmed in the SaTIS trials (Safety of Tirofiban in Acute Ischemic Stroke).5 We speculate that tirofiban may be a better option than aspirin for adjunct therapy.

In this study, we aimed to compare the safety and the preliminary efficacy between the alteplase/tirofiban group and the control group with alteplase alone and to plan for a future phase II study.

Methods

The study protocol was approved by the medical ethics committee of Daping Hospital of the Third Military Medical University. All patients were consented before enrollment.

Study design and procedures, including the clinical protocol, drug dosing, and administration details, are described in Methods in the online-only Data Supplement.

Safety Evaluation

A brain computed tomographic or magnetic resonance imaging scan was performed 24 hours and 7 days after alteplase or anytime if patient had signs of neurological deterioration. Intracranial hemorrhage...
findings were classified into 4 categories: hemorrhagic transformation type I or II and parenchymal hemorrhage type I or II. sICH was defined as ≥4-point increase in the NIHSS (National Institutes of Health stroke scale) and a parenchymal hemorrhage (parenchymal hemorrhage type I or II) without alternative explanation(s) for the neurological deterioration.3 Death, cause of death, and any other systemic bleeding complication were recorded.

Outcome Assessments

Early clinical outcomes were assessed at 24 hours after alteplase and at day 7 (or at hospital discharge) by NIHSS. At 24 hours, the clinical outcomes were categorized into 4 types: (1) clinical persistent improvement: any ≥2-point decrease on the NIHSS after treatment compared with baseline without deterioration; (2) deterioration after improvement: any ≥2-point deterioration on the NIHSS after an initial ≥2-point improvement (excluding intracranial hemorrhagic transformation), it was used as a surrogate marker of cerebral arterial reocclusion in this study6; (3) clinical deterioration: any ≥2-point increase in the NIHSS; (4) no changes: <2-point changes (either increase or decrease) in the NIHSS. The long-term outcome was evaluated by modified Rankin scale at 3 months. The favorable outcome is defined as modified Rankin scale of 0 to 1.

Statistical Analysis

Baseline characteristics were summarized with descriptive statistics. The comparison between the alteplase/tirofiban and the matched alteplase group was analyzed by Mann–Whitney U test and χ²/Fisher exact test according to the distribution of the variables. Efficacy outcomes were compared by multiple logistic regression analyses. Adjusted variables were age, sex, baseline NIHSS, onset to treatment time, history of hypertension, atrial fibrillation, and diabetes mellitus. Statistical analyses were conducted with SPSS 19.0.

Results

The baseline clinico-demographic characteristics of the patients are summarized in Table I in the online-only Data Supplement.

Safety

Three patients in the alteplase/tirofiban group and 3 patients in the control group were found to have ICHs on computed tomographic scan within 7 days after enrollment, but none was classified as sICH (Table 1). One patient in the control group died within 24 hours, but no ICH was discovered. Death was caused by the failed recanalization. One patient in alteplase/tirofiban group died at 2 months because of heart failure.

Efficacy

At 24 hours, 35 (85.4%) patients had clinical persistent improvement in the alteplase/tirofiban group compared with 21 (51.2%) patients in the control group. Notably, arterial reocclusion (reflected by deterioration after improvement) occurred in only 1 (2.4%) patient from the alteplase/tirofiban group versus 9 (22.0%) patients from the control group. The incidence of clinical deterioration (P=1.00) or no changes (P=0.319) was not different (Table 2). At day 7 or discharge, the median NIHSS score was significantly lower in

Table 1. Comparison of Safety Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Alteplase+Tirofiban (n=41)</th>
<th>Alteplase (n=41)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sICH in 7 d, n (%)</td>
<td>0</td>
<td>0</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>ICH in 7 d, n (%)</td>
<td>3 (7.31)</td>
<td>3 (7.31)</td>
<td>1.0 (0.19–5.27)</td>
<td>1.00</td>
</tr>
<tr>
<td>HT I, n (%)</td>
<td>1 (2.4)</td>
<td>2 (4.9)</td>
<td>0.488 (0.04–5.60)</td>
<td>1.00</td>
</tr>
<tr>
<td>HT II, n (%)</td>
<td>2 (4.9)</td>
<td>1 (2.4)</td>
<td>2.05 (0.18–23.55)</td>
<td>1.00</td>
</tr>
<tr>
<td>PH, n (%)</td>
<td>0</td>
<td>0</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Systemic bleeds, n (%)</td>
<td>3 (7.31)</td>
<td>3 (7.31)</td>
<td>1.0 (0.19–5.27)</td>
<td>1.00</td>
</tr>
<tr>
<td>Death in 7 d, n (%)</td>
<td>0</td>
<td>1 (2.4)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Death in 3 mo, n (%)</td>
<td>1 (2.4)</td>
<td>1 (2.6)*</td>
<td>0.95 (0.06–15.73)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Fisher exact test were used for between-group difference. CI indicates confidence interval; HT, hemorrhagic transformation; PH, parenchymal hemorrhage; and sICH, symptomatic intracranial hemorrhage.

*Two patients in this group lost to follow-up.

Table 2. Comparison of Efficacy Outcomes at 24 Hours

<table>
<thead>
<tr>
<th>Variables</th>
<th>Alteplase+Tirofiban (n=41)</th>
<th>Alteplase (n=41)</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical persistent improvement, n (%)</td>
<td>35 (85.4)</td>
<td>21 (51.2)</td>
<td>5.56 (1.92–16.05)</td>
<td>6.40 (1.86–22.06)</td>
<td>0.001/0.003</td>
</tr>
<tr>
<td>Deterioration after improvement, n (%)</td>
<td>1 (2.4)</td>
<td>9 (22.0)</td>
<td>0.09 (0.01–0.74)</td>
<td>0.09 (0.01–0.74)</td>
<td>0.014/0.025</td>
</tr>
<tr>
<td>Clinical deterioration, n (%)</td>
<td>0 (0)</td>
<td>2 (4.9)</td>
<td>...</td>
<td>...</td>
<td>0.494/1.000</td>
</tr>
<tr>
<td>No changes, n (%)</td>
<td>5 (12.2)</td>
<td>9 (22.0)</td>
<td>0.49 (0.15–1.63)</td>
<td>0.49 (0.12–1.98)</td>
<td>0.240/0.319</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and OR, odds ratio.

*Adjusted for age, sex, baseline National Institutes of Health stroke scale, symptom onset to treatment, history of hypertension, atrial fibrillation, and diabetes mellitus.
the alteplase/tirofiban group (1 versus 6; \( P=0.002 \); Figure). At 3 months, 29 (70.7%) patients of the alteplase/tirofiban group compared with 18 (46.2%) patients of the alteplase group had favorable outcomes with modified Rankin scale of 0 to 1 (\( P=0.026 \); Figure II in online-only Data Supplement).

### Discussion

In this proof-of-concept study, we found that the combined alteplase and tirofiban strategy is safe, feasible, and potentially efficacious with improved outcomes when compared with a matched alteplase-alone group. Risks of sICH, all-cause deaths, and systemic bleedings are equivalent between the 2 groups. At 24 hours, fewer patients in the alteplase/tirofiban group had DFI suggesting arterial reocclusion. This favorable outcome sustained to day 7, as well as at 3 months.

The low incidence of sICH was because of a multimodal computed tomographic finding based patient screen process, which theoretically decreases the risk of sICH and the overall improvement of stroke cares in the last decade. This is consistent with other glycoprotein IIb/IIIa studies. The CLEAR-ER study (The Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke-Enhanced Regimen) demonstrated the safety of low dose of alteplase (0.6 mg/kg) plus eptifibatide (135 mg/kg bolus followed by a 2-hour infusion at 0.75 mg/kg/min) for acute ischemic stroke patients within 3 hours of symptom onset.7 Comparing these results with the matched alteplase patients in the NINDS rt-PA stroke trial (National Institute of Neurological Disease and Stroke), the Albumin in Acute Stroke Part 2 trial and Interventional Management of Stroke III demonstrated that alteplase plus eptifibatide showed signs of favorable effect. More recently, the safety of full dosage of alteplase plus eptifibatide was further demonstrated.8,9

There are several limitations of this study. First, it is an open-label, nonrandomized study in 1 academic stroke center. The results were compared with a propensity score–matched historical cohort with alteplase alone. The results need to be interpreted with caution, but the goal of this study is to collect preliminary data for a future phase II study. Second, patients and investigators were not blinded, which may have introduced bias for efficacy and safety outcome assessments. Third, we did not use neuroimaging to confirm the arterial reocclusion or recanalization. Instead, we used clinical assessment as a surrogate measure, which may have room for errors.

In summary, it seems to be safe and feasible to treat selected acute ischemic stroke patients with full dose of alteplase followed by intravenous tirofiban. Such treatment may lead to improvement in outcomes. These results provide useful preliminary data to plan a phase II clinical trial.

### Sources of Funding

This study was funded by Chongqing Science and Technology Grant CSTC2015shmszx120089.

### Disclosures

None.

### References


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SUPPLEMENTAL MATERIAL

Safety and Preliminary Efficacy of Early Tirofiban Treatment after Alteplase in Acute Ischemic Stroke Patients

eMethods: Additional information on study design and procedures

eFigure I: Cases with AIS meeting the multimodal image inclusion criteria.

eFigure II: Distribution of mRS scores at 3 months post-stroke (mRS 0-1)

eTable I: Patients’ Demographic and Clinical Characteristics
eMethods:
The single-center study conducted at our local stroke center. The study protocol was approved by the medical ethics committee of Daping Hospital of the Third Military Medical University. All of patients were consented before enrollment.

Study Design and Procedures:
Forty-one patients with acute ischemic stroke were enrolled between January 2014 and August 2015. The patients were prospectively treated in an open-label, non-randomized protocol of intravenous Alteplase (0.9mg/kg) thrombolysis immediately followed by intravenous tirofiban infusion. All of patients will be assessed at baseline, 24 hours after Alteplase, day 7 or hospital discharge and day 90 post-stroke.

At admission, all patients received an acute stroke computed tomography (CT) protocol using a 256-slice CT (Philips Brilliance iCT, Philips Healthcare, Cleveland, USA), including computed tomography angiography (CTA) and computed tomography perfusion (CTP), cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to peak (TTP). The penumbra is visually identified by the pattern of prolonged MTT and preserved CBV. The infarct core is visually identified by prolonged MTT and decreased CBV.12

The inclusion criteria is as followed: 1) ≥ 18 years old, 2) sudden onset of acute ischemic stroke with symptom onset to treatment (OTT) ≤ 4.5 hours; 3) 4 ≤ admission NIHSS score ≤ 18; 4) a large artery occlusion with the region of decreased CBV less than one third of the region showing a prolonged MTT on CTP; or occlusion in arterioles confirmed by additional MR scan; and 5) patient or LAR is willing to provide a written informed consent (eFigure I).

The exclusion criteria are: 1) pre-stroke mRS ≥ 2; 2) presumed stroke etiology of septic embolism; 3) a recent surgery or trauma, or other active or recent serious systemic hemorrhage; 4) known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency, or taking oral anticoagulant with INR > 1.7; 5) a serum glucose level ≤ 50 mg/dl; 6) having serious, advanced, or terminal illness; or 7) any intracranial hemorrhage detected on CT scan immediately after Alteplase infusion.

A CT scan was done immediately after Alteplase to rule out any ICH. Patient was subsequently consented by him/herself or legal representative. Tirofiban was administered in a body-weight-adjusted dosage with a bolus of 0.4 μg/kg body weight per minute for 30 minutes followed by a continuous infusion of 0.1μg/kg body weight per minute for at least 24 hours.

A historic control (ie. Only intravenously treated with Alteplase 0.9mg/kg) was identified with a propensity score 1:1 matching algorithm.3 The major matching criteria is based on age, sex, baseline NIHSS score, the symptom onset to treatment time(OTT) which were considered as key variables to ensure the balances between the two groups. The historic control group was a cohort that was treated with Alteplase only between March 2013 and August 2015 in the same hospital.
Reference:


eFigure I. Cases with AIS meeting the multimodal image inclusion criteria

Large Vessel Occlusion with penumbra (A): CTA showed an occlusion in LMCA. CTP showed significant prolonged MTT without significantly decreased CBV; Occlusion in arterioles (B,C,D): lenticulostriate artery (B), anterior choroidal artery(C) and perforator of basilar artery (D).

LMCA: left middle cerebral artery; CTA: computed tomography angiography; CTP: computed tomography perfusion; MTT: mean transit time; CBV: cerebral blood volume.
eFigure II: Distribution of mRS scores at 3 months post-stroke

P value is based on Mann-Whitney U test. More patients in the alteplase+ tirofiban group had favorable clinic outcomes (mRS of 0-1) -- 29 (70.7%) patients of the alteplase+ tirofiban group vs. 18 (46.2%) patients of the alteplase only group (P = 0.026; adjusted odds ratio: 4.64; 95% CI: 1.36-15.85).
eTable I. Patients’ Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Alteplase+ Tirofiban (n=41)</th>
<th>Alteplase (n=41)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (range)</td>
<td>66 (29-86)</td>
<td>68 (37-86)</td>
<td>0.141</td>
</tr>
<tr>
<td>Males, n(%)</td>
<td>25 (61.0)</td>
<td>24 (58.5)</td>
<td>0.822</td>
</tr>
<tr>
<td>History of hypertension, n(%)</td>
<td>26 (63.4)</td>
<td>22 (53.7)</td>
<td>0.370</td>
</tr>
<tr>
<td>History of mellitus diabetes, n(%)</td>
<td>14 (34.1)</td>
<td>8 (19.5)</td>
<td>0.135</td>
</tr>
<tr>
<td>Coronary heart disease, n(%)</td>
<td>6 (14.6)</td>
<td>5 (12.2)</td>
<td>0.746</td>
</tr>
<tr>
<td>Atrial fibrillation, n(%)</td>
<td>5 (12.2)</td>
<td>6 (14.6)</td>
<td>0.746</td>
</tr>
<tr>
<td>Current smoker, n(%)</td>
<td>9 (22.0)</td>
<td>7 (17.1)</td>
<td>0.577</td>
</tr>
<tr>
<td>Previous TIA, n(%)</td>
<td>6 (14.3)</td>
<td>1 (2.4)</td>
<td>0.109</td>
</tr>
<tr>
<td>Cholesterol, mean+SD, (mmol/L)</td>
<td>4.48±1.52</td>
<td>4.93±1.68</td>
<td>0.290</td>
</tr>
<tr>
<td>Low Density Lipoprotein, (mmol/L)</td>
<td>2.23±1.18</td>
<td>2.09±1.05</td>
<td>0.626</td>
</tr>
<tr>
<td>Admission NIHSS , median (range)</td>
<td>8 (4-18)</td>
<td>10 (4-18)</td>
<td>0.335</td>
</tr>
<tr>
<td>Symptom onset to IV alteplase, (min)</td>
<td>147.9±27.8</td>
<td>152.6±48.4</td>
<td>0.963</td>
</tr>
<tr>
<td>Responsible artery, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>1 (2.4)</td>
<td>2 (4.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>18 (43.9)</td>
<td>15 (36.6)</td>
<td>0.499</td>
</tr>
<tr>
<td>Arterioles</td>
<td>22 (53.7)</td>
<td>24 (58.5)</td>
<td>0.656</td>
</tr>
</tbody>
</table>

Mann-Whitney U test or Chi-square, or Fisher’s exact test were used to test the difference between groups as appropriate.