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Early administration of tirofiban after urokinase-mediated intravenous thrombolysis reduces early neurological deterioration in patients with branch atheromatous disease

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Abstract

Objectives: To investigate the effects of early administration of tirofiban after intravenous thrombolysis on early neurological deterioration in patients with branch atheromatous disease.

Methods: We analyzed clinical data from patients with branch atheromatous disease. We enrolled seven cases into the urokinase-only (UO) control group and 10 cases into the urokinase + tirofiban (UT) treatment group. National Institutes of Health Stroke Scale (NIHSS) scores were obtained at admission and on days 3 and 5 after admission. Modified Rankin Scale (mRS) scores were obtained 3 months after admission.

Results: Significant differences between the UO and UT groups were evident on days 3 and 5 after admission. In the UT group, there was a significant difference between NIHSS scores at admission and on day 5, while there were no significant differences in scores in the UO group. The early neurological deterioration rates were not significantly different between the two groups. However, there were significant differences in these rates at 72 and 120 hours. Both the mRS scores and the prognoses at 3 months differed between the two groups.

Conclusion: Early administration of tirofiban after urokinase-mediated intravenous thrombolysis reduces early neurological deterioration and improves the long-term prognosis of patients with branch atheromatous disease.

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Introduction

Branch atheromatous disease (BAD) is a kind of ischemic stroke that is characterized by unique features on magnetic resonance imaging (MRI) and progressive motor deficits in the early phase.[1] BAD is diagnosed based on pathological evidence of occlusion or stenosis.[2] The main arteries affected by BAD include the lenticulostriate artery, the pontine paramedian artery, and the anterior choroidal artery.[3] BAD was first defined by Caplan, who emphasized that cerebral infarction caused by BAD differs pathologically from the lipid hyaline degeneration that is characteristic of lacunar infarction.[4] It has been reported that BAD is closely associated with early neurological deterioration (END).[5,6] Patients with BAD may develop severe neurological deficits and have poorer functional outcome.[7,8] One study of 1,458 patients with acute ischemic stroke found that the incidence of BAD was 9.74%, while the frequency of BAD-associated END was 39.4%.[9] The overall incidence of END ranges from about 20% to 58% in acute stroke patients.[10,11] The exact mechanisms of BAD-associated END remain unclear, but have been suggested to involve local thrombosis, local blood–brain barrier disruption, edema, inflammation, and excitotoxicity.[12] It has been reported that the combined treatment of cilostazol, edaravone, and clopidogrel improves functional outcomes in BAD patients; this improvement is likely a result of the vasodilation and endothelial protection functions of cilostazol, the inhibition of shear-induced platelet activation by clopidogrel, and the scavenging of free radicals by edaravone.[13–15] A previous study found that intravenous recombinant tissue plasminogen activator (rt-PA) thrombolytic therapy did not improve BAD-associated END or BAD prognosis.[16] Therefore, an effective BAD treatment is urgently required.

Tirofiban is a GPIIb/IIIa receptor antagonist that can reversibly bind to GPIIb/IIIa receptors to prevent thrombosis. The intravenous infusion of tirofiban in the acute phase of cerebral infarction does not increase the incidence of intracranial hemorrhage, making it a relatively safe treatment. However, although tirofiban administration can reduce mortality rates, it does not improve neurological functional outcomes.[17,18] A randomized, double-blind trial of tirofiban in 150 patients with ischemic stroke within 6 hours of onset revealed a 72-hour improvement in neurological function in both the tirofiban and the aspirin groups. However, there were no significant differences in either mortality or the proportion of patients with good outcomes at 3 months, and the incidence of symptomatic intracranial hemorrhage was 1% in the tirofiban group and 4% in the aspirin group.[18] Next, studies were performed investigating the combined application of tirofiban with thrombolytic therapy for cerebral infarction.[19,20] Combined tirofiban and rt-PA treatment in the acute phase of cerebral infarction did not increase the incidence of intracranial hemorrhage, but significantly improved neurological functional outcomes (as measured by the National Institutes of Health Stroke Scale [NIHSS] and Modified Rankin Scale [mRS] scores). In 51 patients with cerebral infarction who started intravenous infusion of

tirofiban within 24 hours of rt-PA intravenous thrombolysis, neurological functional outcomes were significantly improved compared with patients who received rt-PA only. Furthermore, tirofiban did not increase symptomatic intracranial hemorrhage, death, or systemic hemorrhage, but NIHSS scores at 7 days or discharge were decreased and better neurological functional outcomes were noted at 3 months (mRS = 0–1).[20] However, the effect of treatment with tirofiban alone, or in combination with urokinase-mediated intravenous thrombolysis, has not yet been reported on the early outcomes and long-term prognoses of BAD patients. Therefore, in the present study, we prospectively investigated the effects of early intravenous thrombolytic therapy with urokinase, with or without tirofiban, on the early outcomes and long-term prognoses of BAD patients.

Materials and methods

Patients

From June 2017 to February 2019, we prospectively collected data on BAD patients treated at the Suzhou First People's Hospital. Patients were enrolled in a urokinase-only (UO) control group or a urokinase + tirofiban (UT) treatment group. The treatment protocol was chosen in accordance with the "Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke in China 2014", which states that if the onset of stroke is within 6 hours, intravenous urokinase can be used for patients who meet the indication and contraindication requirements. The indications included: 1) neurological deficits caused by ischemic stroke; 2) symptom onset <6 hours before treatment; 3) 18 to 80 years old; 4) conscious or lethargic; 5) brain computed tomography (CT) revealed no obvious early cerebral infarction low-density changes; 6) informed consent was signed by the patient or their family members. The inclusion criteria were as follows: 1) the patient met the standards for urokinase intravenous thrombolysis in the "Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke in China 2014", and was administered urokinase intravenous thrombolysis; 2) the dose of intravenous thrombolytic urokinase was 1 million U; 3) after intravenous thrombolysis with urokinase, re-examination of brain CT showed no bleeding in the brain and there was no systemic bleeding in other parts of the body. No patients evidenced intracranial or systemic bleeding. All patients met the BAD diagnostic criteria,[7] which were as follows: intracerebral lesions with a diameter of $\geq$15 mm, and more than three slices or lesions extending to the surface of the pontine base. Head MRI and magnetic resonance angiography examinations were completed within 48 hours of admission. The exclusion criteria were as follows: a prior history of stroke and a failure to continue tirofiban treatment for 48 hours. One patient was excluded from the study because his clinical symptoms did not improve after the application of tirofiban and he was concerned about the possible bleeding risk. Using the 3-month mRS scores, patients were divided into those exhibiting good prognoses (mRS scores $\leq$1) and those exhibiting poor prognoses (mRS scores $\geq$2). The experimental protocol was approved by the Ethics Committee of Suzhou First Peoples' Hospital (no. SZ2017GG48). Written consent was obtained from each patient or their parent/caregiver.

Treatments

All patients underwent intravenous thrombolytic therapy (using 1 million U of urokinase) after admission. Patients in the experimental group also received tirofiban

(50 mL; 12.5 mg; Lunan Hengkang, Lunan Pharmaceutical Co. Ltd., Shandong, China). After intravenous thrombolysis with urokinase, a head CT scan was routinely performed to exclude intracranial hemorrhage. Tirofiban hydrochloride was infused at 0.4 μg/kg/minute for 30 minutes, and then at 0.1 μg/kg/minute for 47 hours and 30 minutes. Four hours before the end of tirofiban infusions, patients were started on antiplatelet treatment (100 mg aspirin and 75 mg clopidogrel daily by oral administration). Twenty-one days later, the treatment was changed to only 100 mg aspirin daily. In the control UO group, the antiplatelet therapy procedure was as follows: 100 mg aspirin combined with 75 mg clopidogrel given orally at 24 hours after intravenous thrombolysis. After 21 days of dual antiplatelet therapy, 100 mg aspirin only was administered daily. The conventional treatment (urokinase-mediated thrombolysis) followed the Chinese guidelines for the diagnosis and treatment of acute ischemic stroke (2014 version).

Head CT was performed at four time points: 1) immediately after urokinase intravenous thrombolysis was completed; 2) when 100 mg aspirin and 75 mg clopidogrel were administered orally 4 hours before the end of tirofiban infusions; 3) when there were changes in a patient's condition within 7 days after hospitalization; 4) on day 7 of hospitalization. NIHSS scores were obtained at admission and on days 3 and 5 after admission. mRS scores were obtained at 3 months after admission. END was considered to be present if the difference between an NIHSS score and the lowest earlier score was ≥ 2.

Statistical analyses

Statistical analyses were performed using SPSS Version 22.0 (IBM Corp., Armonk, NY, USA). Qualitative data are expressed as rates and were compared using the chi-squared or Fisher's exact test. Quantitative data that were normally distributed are expressed as means ± standard deviations. Ordered data were subjected to a Mann–Whitney *U* test. The NIHSS scores at different time points were compared using repeated measures analysis of variance. The incidence of END at different time points was compared using generalized estimating equations. A P-value < 0.05 was taken to indicate statistical significance.

Results

Demographic data

We enrolled 17 cases: seven in the UO control group and 10 in the UT treatment group. Demographic data are shown in Table 1. The control group contained four men and three women, aged 64.71 ± 10.48 years, of whom six had hypertension (85.71%) and two had diabetes (28.57%). The treatment group contained four men and six women, aged 58.50 ± 9.03 years, of whom eight had hypertension (80.00%) and two had diabetes (20.00%). The average blood glucose and low-density lipoprotein were measured at admission, and the onset-to-treatment time (OTT) was calculated. There were no significant differences in any of these baseline data between the two groups (Table 1).

Comparison of early neurological deterioration

Neurological deterioration data are shown in Table 2. The extent of neurological deterioration over the first 24 hours after admission (END1 scores) did not differ between the two groups (UO group: four cases [57.14%], UT group: four cases [40.00%]). However, the extent of neurological deterioration over the first 72 hours after admission (END3 scores) was significantly different between the two groups (UO

Table 1. Comparison of general clinical data between the groups.

	Urokinase group	Urokinase + tirofiban group	x^2	*P*
Sex (male/female)	4/3	4/6	–	0.637
Age (years)	64.71 ± 10.48	58.50 ± 9.03	1.308	0.211
High blood pressure (*n*/%)	6/85.71	8/80.00	–	1.000
Diabetes (*n*/%)	2/28.57	2/20.00	–	1.000
Blood glucose at admission (mmol/L)	10.43 ± 6.45	8.96 ± 3.51	0.608	0.552
Low density lipoprotein (mmol/L)	2.58 ± 1.12	3.38 ± 0.93	−1.601	0.130
OTT (h)	3.31 ± 0.87	3.05 ± 1.40	0.431	0.673

OTT: onset to treatment time. Qualitative data are expressed as rates and were compared using the chi-squared or Fisher's exact test; quantitative data were compared using the Mann–Whitney *U* test.

Table 2. Comparison of early neurological deterioration between groups.

	Urokinase	Urokinase + tirofiban	OR (95%CI)	*P*
END1d (*n*/%)	4/57.14	4/40.00	0.500 (0.070–3.550)	0.637
END3d (*n*/%)	6/85.71	1/10.00	0.019 (0.001–0.357)	0.004
END5d (*n*/%)	6/85.71	2/20.00	0.042 (0.003–0.574)	0.013

OR: odds ratio; CI: confidence interval; END1d: early neurological deterioration on day 1; END3d: early neurological deterioration on day 3; END5d: early neurological deterioration on day 5. Qualitative data are expressed as rates and were compared using the chi-squared or Fisher's exact test.

group: six cases [85.71%], UT group: one case [10.00%]), as was the extent of neurological deterioration over the first 120 hours (END5 scores; UO group: six cases [85.71%], UT group: two cases [20.00%]).

Comparison of NIHSS scores at early stages

The NIHSS scores are shown in Table 3. There were no significant differences between the two groups at admission (UO group: 7.29 [5.00, 9.00], UT group: 7.00 [4.00, 9.25]). However, significant differences were evident on days 3 (UO group: 6.71 [4.00, 11.00], UT group: 3.30 [1.00, 4.50]) and 5 (UO group: 5.57 [3.00, 9.00], UT group: 2.60 [1.75, 4.25]) after admission. In the control group, the scores at admission and at day 5 did not differ; in contrast, they were significantly different in the test group.

Comparison of prognosis and mRS scores at 3 months

The prognosis and 3-month mRS scores are shown in Table 4. The prognoses were significantly different between the two groups (good prognosis: one UO patient, eight UT patients; poor prognosis: six UO patient, two UT patients). The between-group difference in 3-month mRS scores was also significant (UO group: 2.86 [2.00, 4.00), UT group: 1.00 [0.00, 1.50]).

Discussion

This study revealed that intravenous urokinase thrombolysis improved neurological deficits in patients with BAD over a short period of time, but that neurological function soon deteriorated. However, urokinase combined with tirofiban resulted in the continued improvement of neurological function over a longer period. Thus, the early

Table 3. Comparison of early NIHSS scores between groups.

	NIHSS at admission	3dNIHSS	5dNIHSS	$Z^{\#}$	*P*
Urokinase group (M (P25, P75))	7.29 (5.00, 9.00)	6.71 (4.00, 11.00)	5.57 (3.00, 9.00)	–1.886	0.059
Urokinase + tirofiban group (M (P25, P75))	7.00 (4.00, 9.25)	3.30 (1.00, 4.50)	2.60 (1.75, 4.25)	–2.670	0.008
Z^*	0.000	–2.114	–2.085		
P	1.000	0.035	0.037		

NIHSS: National Institutes of Health Stroke Scale; 3dNIHSS: NIHSS at day 3; 5dNIHSS: NIHSS at day 5; M: median; P25: 25th percentile; P75: 75th percentile. *Mann–Whitney *U* test was applied between groups; #signed rank test was applied within the group.

Table 4. Comparison of long-term prognosis between groups.

	Prognosis		
	Good	Poor	3mmRS
Urokinase	1	6	2.86 (2.00, 4.00)
Urokinase + tirofiban	8	2	1.00 (0.00, 1.50)
OR (95% CI)	0.042 (0.003–0.574)		–
Z/x^2	–		–2.108
P	0.015		0.043

3mmRS: Modified Rankin Scale at 3 months; OR: odds ratio; CI: confidence interval. Qualitative data are expressed as rates and were compared using the chi-square or Fisher's exact test; quantitative data were compared using the Mann–Whitney *U* test.

joint application of urokinase and tirofiban is critical to reduce the risk of END in patients with BAD. There was also a significant difference in prognosis between the two groups, suggesting that urokinase combined with tirofiban can also improve the long-term prognosis of patients with BAD.

Globally, low- and middle-income countries bear most of the stroke burden.[21] Intravenous thrombolysis using rt-PA is expensive, and is thus often unavailable in economically underdeveloped areas; the use of urokinase has economic advantages. Several studies have reported that rt-PA does not reduce END in BAD patients or enhance 3-month mRS scores.[9,22] In addition, Deguchi et al.[11] evaluated eight BAD patients who underwent rt-PA intravenous thrombolysis over a 5-year interval. Six (75%) exhibited improved neurological function within 1 hour after intravenous thrombolysis, but 4 (67%) had worsened neurological function within 24 hours and two (25%) had 3-month mRS scores of 3 to 6. These results suggest that rt-PA temporarily improves BAD symptoms, but the extent of later symptom deterioration remains high. In the present study, urokinase did not improve the early NIHSS scores of BAD patients; four (57.14%) had neurological deterioration within 24 hours of intravenous thrombolysis. Such patients, as well as those who deteriorate after conventional therapy, are very difficult to treat. An early effective treatment is therefore urgently needed. In our study, combined treatment with tirofiban administration and intravenous thrombolysis resulted in significantly different rates of neurological deterioration over 72 (END3

scores) and 120 hours (END5 scores) compared with UO controls, indicating that early administration of tirofiban and intravenous thrombolysis can effectively reduce END in patients.

Antiplatelet therapy may effectively counter both BAD and END. Yamamoto et al.[16] prescribed combined antiplatelet therapy for 313 BAD patients treated over 12 years, and found that cilostazol was more effective for those with basilar artery diameters of 200 to 300 μm, whereas clopidogrel was more effective for those with bean-shaped arteries with diameters of 700 to 800 μm. Furthermore, Kimura et al.[14] studied 144 BAD patients given cilostazol plus aspirin or clopidogrel within 12 hours of disease onset and found that, compared with single antiplatelet therapy (aspirin or clopidogrel or cilostazol), early combined cilostazol-based antiplatelet therapy significantly reduced END. Platelet activation may thus be involved in the pathophysiology of BAD, and may help to explain END. Yokote et al.[23] reported that the platelet activation markers β-platelet globulin and platelet factor 4 had significantly elevated levels in BAD patients. Moreover, Oji et al.[1] investigated 64 BAD patients and revealed that a high mean platelet volume at admission was an independent risk factor for END; BAD patients with an average platelet volume >10.1 fL at admission were at high risk for END. In addition, Staszewski et al.[24] studied 237 patients with ischemic stroke and reported that patients undergoing intravenous thrombolysis who had high mean platelet counts were at greater risk for morbidity and mortality. Mean platelet volume is therefore an independent predictor of poor prognosis in ischemic stroke patients treated via intravenous thrombolysis. Platelet volume is positively correlated with the extent of platelet aggregation and expression levels of the platelet glycoprotein IIb/IIIa receptor.[25,26] When inhibitors of this receptor are activated by adenosine diphosphate, adrenaline, collagen, or thrombin, they inhibit the expression of fibrinogen, von Willebrand factor, fibronectin, and vitronectin, thus directly reducing platelet aggregation by blocking the final aggregation step.[27]

Tirofiban hydrochloride is a common and widely used inhibitor of the platelet glycoprotein IIb/IIIa receptor. Liu et al.[28] observed that tirofiban combined with rt-PA is beneficial in acute ischemic stroke when administered at 2 to 12 hours after intravenous thrombolysis, suggesting that the time of tirofiban administration is important. In the present study, the early combination of urokinase-mediated intravenous thrombolysis and tirofiban hydrochloride administration improved the 3-month mRS scores in BAD patients, meaning that patient prognoses were significantly improved by this treatment. This result is consistent with those of some previous studies. Recently, BAD pathogenesis has been investigated using high-resolution MRI. Liao et al.[29] studied 32 patients with anterior-circulation BAD and found that, compared with patients with lacunar infarctions, BAD patients exhibited a greater extent of injury in the middle cerebral artery region, larger atherosclerotic plaques, and heavier plaque loads. Furthermore, Sun et al.[30] reported that 15 BAD patients (46.9% of the study population) had atherosclerotic plaques in the middle cerebral artery region as well as longer and larger cerebral infarctions. In another study, low-dose tirofiban did not increase the risk of symptomatic intracranial hemorrhage or mortality, but improved neurological outcomes at 3 months, which is consistent with the results from our study.[31] These results reveal that macrovascular atherosclerosis is very important in terms of BAD pathogenesis, and that antiplatelet agents play important roles in the prevention and progression of atherosclerotic plaques.

In summary, we revealed that the early administration of tirofiban after urokinase-mediated intravenous thrombolysis led to reduced END and improved long-term prognosis in patients with BAD. Combined urokinase-mediated thrombolysis and tirofiban administration is therefore useful in clinical practice. Our results indicate that, in a clinical situation, early administration of tirofiban and urokinase may induce better early neurological outcomes and long-term prognosis compared with urokinase treatment alone. However, there are several limitations of our study. First, the sample size is relatively small, and more clinical data should be analyzed in the future to better support our conclusions. Second, only one dose and administration time was used in the study, which was chosen following the Chinese guidelines. Various doses and time points of drug administration can be explored in the future. Nevertheless, the present study adds a new dimension to our understanding of the effects on END of early tirofiban administration after urokinase-mediated intravenous thrombolysis, and supports the potential value of this treatment for clinical application.

Availability of materials

All the materials in this study can be obtained from the corresponding author upon reasonable request.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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