SAFETY OF TIROFIBAN FOR PATIENTS WITH ACUTE ISCHEMIC STROKE IN ROUTINE CLINICAL PRACTICE

Yan-Jun Zhang, Qing Liu, Qin Zhan, Qiong Li

Aim. This work aims to study the safety of tirofiban alone and in combination with various treatments in acute ischemic stroke (AIS).
Material and methods. 120 AIS patients were included in this study. There were 3 groups as below: Group A (tirofiban alone, n=68), Group B (tirofiban plus thrombolytic therapy, n=26), and Group C (tirofiban plus bridging therapy, n=26). Risk factors, stroke severity, initial imaging, treatment regimens, complications and long-term outcomes were analyzed.
Results. Eight patients (6,7%) in Group A, 6 patients (23,1%) in Group B and 2 patients (7,7%) in Group C had hemorrhage during or after treatment. Sixteen patients (6 in Group A, 8 in Group B and 2 in Group C) died during hospital admission. The mortality rate was 13,3% (8,8% for Group A, 30,7% for Group B and 7,7% for Group C, respectively) in the acute phase. A favorable outcome (mRS 0–2) at the first three months after stroke was only observed in 43,3% of patients (44,1% in Group A, 46,7% in Group B and 36,4% in Group C). The average Barthel index was 72,3 in Group A, 84,4 in Group B and 56,8 in Group C (total score: 71,0).
Conclusion. The stroke treatment with tirofiban is safe in AIS. A large randomized controlled trial in the future will be needed to decrease the minor bleeding complication of tirofiban therapy.

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Key words: Tirofiban, acute ischemic stroke, safety.

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AIS — acute ischemic stroke, BI — Barthel Index, CCTs — cerebral CT-built, CEA — carotid endarterectomy, CTA — CT angiography, DSA — digital Subtraction angiography, GFAP — glial fibrillary acidic protein, ICA — internal carotid artery, MRA — magnetic resonance angiography, mRS — Modified Rankin Scale, NIHSS — National Institutes of Health Stroke Scale, PTCA — percutaneous transluminal coronary angioplasty, tPA — plasminogen activator, UFH — unfractionated IV heparin.

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БЕЗОПАСНОСТЬ ТИРОФИБАНА ДЛЯ ПАЦИЕНТОВ С ОСТРЫМ ИШЕМИЧЕСКИМ ИНСУЛЬТОМ В РУТИННОЙ КЛИНИЧЕСКОЙ ПРАКТИКЕ

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Цель. Данная работа направлена на исследование безопасности применения одного тирофибана и в сочетании с различными препаратами в острый период ишемического инсульта (ОИИ).
Материал и методы. 120 пациентов с ОИИ были включены в это исследование. Они были разделены на 3 группы: Группа А (тирофибан, n=68), группа б (тирофибан плюс тромболитическая терапия, n=26), и группа С (тирофибан плюс сопутствующее лечение, n=26). Факторы риска, степень тяжести инсульта, первичное обследование, схемы лечения, осложнений и долгосрочные результаты были проанализированы.
Результаты. Восемь пациентов (6,7%) в группе, у 6 (23,1%) в группе В и 2 пациентов (7,7%) в группе С, были кровотечения во время или после лечения. Шестнадцать пациентов (6 в группе А, 8-в группе В и 2 в группе С) умерли во время госпитализации. Уровень смертности составил 13,3% (8,8% для группы А, 30,7% для группы В и 7,7% для группы С, соответственно) в фазе обострения. Благоприятный исход (mRS 0–2) в первые три месяца после инсульта наблюдался только в 43,3% пациентов (44,1% в группе А, 46,7% в группе В и 36,4% в группе С). Средний Barthel index был 72,3 в группе А, 84,4 в группе В и 56,8 группы С (Общая оценка: 71,0).
Вывод. Лечение инсультов с применением тирофибана безопасно при ОИИ. Большие рандомизированные контролируемые испытания будут необходимы в будущем для уменьшения незначительных кровотечений как осложнений терапии тирофибаном.

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Ключевые слова: тирофибан, острый ишемический инсульт, безопасность.

Acute ischemic stroke (AIS) is a common cause of morbidity and mortality worldwide. Thrombolysis with recombinant tissue plasminogen activator is the only proven beneficial therapy in AIS which is received by less than 2% of patients [1]. The reasons include lack of adequate transport facilities, high cost of tissue plasminogen activator, lack of proper infrastructure including facilities for thrombolysis in most centers, and lack of awareness among public and doctors [2]. Moreover, there is a slight increase in hemorrhagic complications with thrombolysis.

Glycoprotein IIb/IIIa inhibitors, after their initial success in patients with acute coronary syndromes, has led to increasing interest to treat AIS over the past decade [3–7]. Highly selective platelet antagonists, the glycoprotein (gp) IIb/IIIa inhibitors, block the fibrin binding receptors reversibly and effectively prevent platelet aggregation. Tirofiban is a fast-acting, highly selective nonpeptide gpIIb/IIIa antagonist for the treatment of acute coronary syndrome up to 48 hours after onset [5].

However, the exact effect of tirofiban in patients with AIS, including risk factors, stroke severity, treatment regimens, complications, symptomatic or asymptomatic hemorrhage and long-term outcomes are unclear at the moment. The aim of this research was to study the safety of tirofiban alone and in combination with various treatments in AIS.

Materials and methods

Patients. A total of 120 patients with AIS, 70 men and 50 women, in the context of individual treatment trial with tirofiban were included in the study. Patient Inclusion and Exclusion Criteria-Patients with ischemic stroke between

18 and 82 years who were not eligible for thrombolysis and within a timeframe of 45 to 72 hours after onset of symptoms with National Institutes of Health Stroke Scale (NIHSS) scores between 4 and 18 were recruited. Patients were excluded if platelet level was <100 000/μL or there were contraindications to anticoagulants/thrombolytic agents. Prophylactic doses of low-molecular-weight heparin as deep vein thrombosis prophylaxis are allowed but higher doses were not. Pregnant women, subjects disabled before the recent stroke (modified Rankin Scale>2), recently treated with thrombolysis, or with recent major bleedings, surgery, or trauma were excluded. All patients received a first brain imaging (CT or MRI), blood pressure monitoring as well as laboratory tests (platelet counts, partial prothrombin time, creatinine, hemoglobin) before randomization. Hypertension was defined as on prior medication or elevated initial blood pressure during screening (systolic blood pressure >160 mm Hg). Hypercholesterolemia was classified as patients on lipid-lowering substances as well as diabetes on antidiabetics.

This study was approved by Ethics Committee of Zhengzhou People's Hospital in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Treatment. An initial dose of 0.4 mg/over 30 kg, and then continued at 0.1 mg/kg body weight per hour. The recommended infusion duration was 24 hours. Here, both patients receiving tirofiban alone and patients receiving tirofiban and other recanalisations methods were included. There were 3 groups: Group A (tirofiban monotherapy), Group B (tirofiban in combination with an intravenous or intra-arterial thrombolysis) and Group C (tirofiban as "bridging therapy", an additional recanalisation measure started before and continued during and after the intervention known as the PTCA and coronary stent implantation).

Data collection. Vascular risk profile, stroke localization, treatment duration, cumulative dose and time of Tirofibandosis were recorded. Modified Rankin Scale (mRS) was used to describe the severity of the stroke.

Pretreatment imaging including cerebral CT-built (CCTs) and stroke MRIs were performed to evaluate infarct demarcation, and early signs of infarction. In patients who had finished angiography before treatment, it should be noted whether a vascular occlusion had happened.

CCTs and MRIs were scored for bleeding complications during and after tirofiban application. To determine the severity of bleeding, ECASS II criteria were used: hemorrhagic infarction 1 (HI1) with small hemorrhages along the infarct margins; hemorrhagic infarction 2 (HI2) on confluent hemorrhage within infarct area but without space-occupying effect; parenchymal bleeding 1 for a bleeding that affects up to 30% of the infarct area and shows a possibly small space-occupying effect; parenchymal bleeding 2 at a blood flow, which affects more than 30% of the infarct area and has a significant space-occupying effect. Symptomatic intracerebral hemorrhage was defined as bleeding in any region of the brain accompanied by a significant clinical deterioration [8]. Among the patients in whom an initial vascular occlusion was documented, were, after treatment by means of representations guided vascular CT angiography (CTA), magnetic resonance angiography (MRA) or digital Subtraction angiography (DSA) evaluated for recanalisation. NIHSS, mRS and Barthel Index (BI) were used to assess the outcomes at discharge.

Statistical analysis. All experiments were performed at least three times. Data were expressed as mean ± standard deviation. One-way ANOVA was used to analyze data. A p value less than 0.05 was considered statistically significant.

Results

General characteristics. There were a total of 120 patients, 70 men and 50 women, who were treated with tirofiban in the context of individual treatment trial. Overall baseline characteristics were similar in all groups; no significant difference was found for age, baseline NIHSS at screening, time between symptom onset, screening, and start of infusion. The proportion of men was higher than that of women in all groups. The vascular risk profile of patients was summarized in Table 1.

Patient groups. Many patients (n=68) received tirofiban as monotherapy and were assigned to Group A. A clot lysis by tissue plasminogen activator (tPA) here was no longer in question mainly because of a lapse three-hour time window. Because the remaining 18 patients were treated within the window time, there were different exclusion criteria for lysis treatment. Two patients suffered from ulcerative colitis, two had an alcohol abuse and another four patients already had the tirofiban treatment. 26 patients above were assigned to Group B. And these 26 patients were also divided into subgroups according to who received tirofiban following a systemic or intra-arterial thrombolysis.

The rest 26 patients were assigned to group C, in which to initiate other recanalisation or bridging IV therapy during the tirofiban therapy. In one case, the bridge was combined with a Carotid endarterectomy (CEA). The young patient was previously treated systemically because of a medium infarction. Since the symptoms were not improved, she was brought to our hospital, where a stenosis of the internal carotid artery (ICA) and a thrombus just distal to the stenosis were determined at the day after admission. Eight patients received IA thrombolysis, which was in the middle period from onset of symptoms until 2.5 hours after the start of treatment. In three patients, however, the time of symptom onset was unclear. The intra-arterial embolectomy was performed in three patients. The time to initiation of treatment with tirofiban was on average 6.25 hours, until another 35 minutes at the

beginning of the intervention. One patient received IV lysis and tirofiban practically and simultaneously, the time of treatment was 2.5 hours. In all patients undergoing neuro-interventional radiology measure, the infusion was maintained during and after treatment by coronary angiography or by percutaneous transluminal coronary angioplasty (PTCA) with or without stent implantation in patients with acute coronary syndrome. The distribution of stroke localization in the different groups was shown in Table 2.

Imaging findings. Prior to treatment, all of the patients received cerebral imaging CT, even MRI in two cases to rule out intracerebral hemorrhage. Thirty-two patients were found the demarcated infarcts in imaging studies; another 24 patients had at least early infarct signs.

93,3% of the patients had also a vascular imaging with CTA, MRA or DSA. Transcranial Duplex Sonography was carried out in two cases. 68 patients (56,7% of total population) had a complete or nearly complete vessel occlusion.

Clinical outcomes and complications. The application of tirofiban was recommended for duration of 24 hours. However, the infusions were generally continued until a stable situation had been established in 12 cases. And there was even a second dose for fluctuating symptoms, so that the total application time significantly extended. The mean treatment duration was 30,5 hours (ranging from 4 to 106 hours). The mean cumulative dose was 15,7 mg tirofiban (ranging from 2,5 to 71,9 mg). The infusion had to be terminated prematurely in 18 patients because of complications. Two cases showed a contrast medium extravasation injury in the basal ganglia by CT imaging after thrombolysis, so that the infusion was stopped because a potential bleedingd by the contrast agent can be masked. Four patients developed a large space-occupying infarction and had to receive hemicraniectomy. There were concerns whether the treatment continue in two cases, since the patient was suffering from colon cancer. Thrombocytopenia occurred in two cases. Two patients had a haematemesis and another four patients had a control parenchymal bleeding at the end of CT.

The time from symptom onset to tirofiban administration was very different and ranged from 45 to 72 hours, especially because many patients in group A were treated only with tirofiban and the fluctuation in symptoms was noticeable. In ten patients, the time of symptom onset could not be determined because the patient woke up with symptoms. The median time was the time to start similar treatment in groups A and C (Table 3).

The four patients, who had been waived on an imaging, had an excellent outcome with complete resolution of symptoms. In the total population, only 8 (6,7%) out of all patients suffered hemorrhage. All hemorrhages were classified as parenchymal bleeding first, and symptomatic bleeding had not occurred. Table 4 shows the frequency of bleeding in each group.

14 patients (11,7%) experienced extracerebral bleeding complications. 10 cases included a gastrointestinal hemorrhage, a hematoma of the abdominal wall, a compartment syndrome after hemorrhage in the thigh. None of the patients required a blood transfusion. 2 out of 14 patients had received tirofiban after a systemic lysis with tPA, the rest 12 patients were treated in group A. The one patient observed in group A had not clinically significant thrombocytopenia.

A complete or nearly complete vessel occlusion had been detected in 68 patients. 38 of them were subjected to transcranial duplex sonography. 24 cases had recanalisation of the occluded vessel (Table 5).

Stoke severity. To assess the severity of the stroke, patients were assessed by modified mRS and NIHSS at admission, shown in Figure 1. The median NIHSS was 11 points in the overall, 8 points, in group A, 16 points in Group B and 12 points in Group C. Overall, the variation was very large, but most cases were the heavy ones.

16 patients (6 in group A, 8 in group B, 2 in group C) died during the hospital stay, which the mortality was 13.3% (8,8% for group A, 30,7% for group B and 7,7% for group C, respectively) in the acute phase. These 16 patients had a mRS 5 at admission. 48 Of the 52 patients or their relatives were interviewed. The follow-up was

Table 1

Vascular risk profile of patients

Risk factors	n (%)
Diabetes mellitus	16 (13,3)
Arterial hypertension	74 (61,7)
Arteriosclerosis	68 (56,7)
Heart rhythm disorders	30 (25,0)
Other cardiac source of embolism	26 (21,7)
Hyperlipidemia	52 (43,3)
Obesity	52 (43,3)
Previous stroke	28 (23,3)
Smoking (current and former)	30 (25,0)

Table 2

The distribution of stroke in the different groups

Infarct	Total, n	Group A, n	Group B, n	Group C, n
Anterior circulation Infarct	36	20	2	14
Posterior circulation Infarct	80	46	22	12
Watersheds Infarct	4	2	2	-

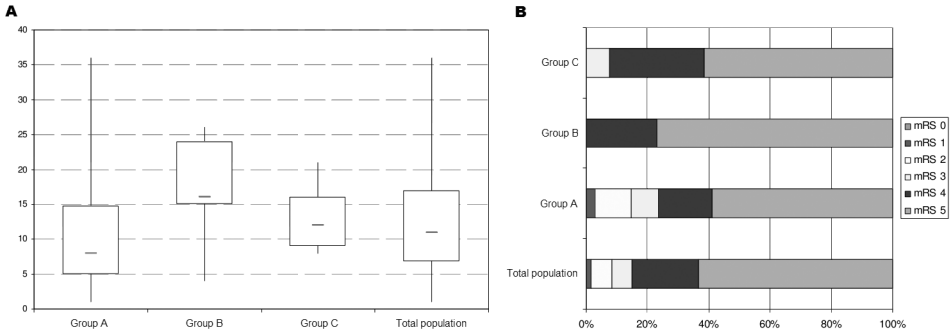

Figure 1. The stoke severity in each group at admission. A) NIHSS; B) mRS.

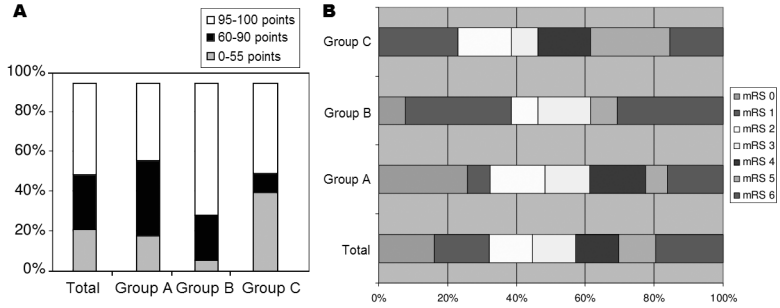

Figure 2. Outcome of patients in each group three months or longer after stroke. A) Barthel Index; B) mRS.

between three and 14 months after the stroke, and Barthel index and mRS were queried. The results were shown in Figure 2.

A favorable outcome (mRS 0–2) at the earliest three months after stroke was only observed in 43,3% of patients (44,1% in group A, 46,7% in group B and 36,4% in group C). The average Barthel index was 72,3 points in group A, 84.4 points in Group B, 56,8 points in Group C and 71,0 points in the overall.

Discussion

In this retrospective study, it was shown that in certain selected cases, the treatment of acute ischemic stroke with the GPIIb/IIIa antagonist tirofibans. This opens up the next thrombolysis with rTPA further treatment options such as a bridge between diagnosis and specific measures for revascularization. The present study is retrospective, however, not controlled and considered various treatment strategies simultaneously, so that we urgently needed to confirm the results of larger prospective, controlled studies.

The studied patient population can be well with group B of the present study compared, in which no symptomatic and only 3% of patients with asymptomatic hemorrhages occurred, although both rtPA and tirofiban was not used in a reduced dose. A follow-up study with rTPA 0.6 mg/kg plus eptifibatide versus standard-lysis in the pipeline. Then will then decide whether it will be a Phase III efficacy study [9].

Interesting results were also found in experimental stroke research in rodents. A dose-dependent relationship between intracerebral hemorrhage risk and use of an anti-mouse GPIIb/IIIa F (ab) 2 fragments could be detected for the dose that resulted in a receptor blockade of more than 95%, but not for the dose at which a receptor blockade was achieved by 67.8% [10]. Choudhri et al. found significant bleeding in maximum doses following administration of non-peptidic substance SDZ GPI 562 in a mouse model of acute ischemic stroke. After administration of lower doses was found after staining with triphenyltetrazolium chloride, a significantly smaller infarct volume than expected [11]. Other studies in experimental stroke models in guinea pigs and squirrel monkeys with the non-peptide GPIIb/IIIa blocker FK419 could uncover no bleeding complications, but showed reduced infarct volume as an indication of their effectiveness [12, 13].

The GPIIb/IIIa receptor (integrin aIIbb3) has the same β3 subunit as the vitronectin receptor (integrin αvβ3) that is present on resting endothelial cells in small numbers. However, the expression of αvβ3 by angiogenic stimuli such as hypoxia, transforming growth factor (TGF) -β3 and thrombin, as they occur in the context of regional cerebral ischemia, upregulated. The expressed on endothelial cell vitronectin receptor is responsible for the adhesion of monocytes to the endothelium, conveys a permeability the blood-brain barrier and contributes as well as the vascular endothelial growth factor (VEGF) on proliferation and migration of inflammatory cells into the perivascular tissue

Table 3

Time to initiation of treatment with tirofiban (hours)

	Total	Group A	Group B	Group C
Average	9,5	11,6	9,3	3,6
Median	4,5	4,25	7,0	2,5

Table 4

The frequency of bleeding in groups

	Total bleeding, n (%)	HI1, n (%)	HI2, n (%)	PH1, n (%)	PH2, n (%)	SICH, n (%)
Total	8 (6,7)	-	-	8 (6,7)	-	-
Group A	-	-	-	-	-	-
Group B	6 (23,1)	-	-	6 (23,1)	-	-
Group C	2 (7,7)	-	-	2 (7,7)	-	-

Table 5

Arterial recanalization rate for all patients diagnosed with vascular occlusion

Therapy	Recanalization, n (%)
Tirofiban-Monotherapy (n=8)	2 (25%)
IV thrombolysis (n=8)	4 (50%)
IA thrombolysis (n=16)	14 (88%)
IV and IA. thrombolysis (n=2)	0 (0%)
Embolectomy (n=4)	2 (50%)
Early CEA (n=2)	2 (100%)
All (n=40)	24 (60%)

during angiogenesis in [14, 15]. Possibly by the binding of GPIIb/IIIa receptor blockers on the vitronectin receptor and the permeability of the blood-brain barrier and thus influences the occurrence of intracerebral hemorrhage. This should bring a dose-dependent study of the effects of GPIIb/IIIa blockers on activated endothelial cells further insight.

While the link between fibronectin receptor interference and occurrence of ICB is currently more of a theoretical nature, the favorable relationship between vascular occlusion and reperfusion after ICB has been shown in several studies [16]. The use of biomarkers in blood-brain barrier provides in predicting intracranial hemorrhagic complications after stroke and especially after thrombolysis followed by additional help. Especially for matrix metalloproteinase-9, cellular fibronectin, S100β and glial fibrillary acidic protein (GFAP) has been shown that they can contribute to the prediction of intracranial hemorrhage [17].

These biomarkers could also be used to study the different GPIIb/IIIa antagonists in regard to bleeding complications. Since the individual substances in structure and mode of action show quite lower vagina, could thus those that are particularly suitable for treating cerebral ischemia, are highlighted. Mangiafico et al. published a paper in which they described 21 patients with acute ischemic stroke who have an aggressive treatment regimen consisting obtained from iv tirofiban for 24 to 48 hours, iv heparin, a local lysis with urokinase and in most patients undergoing percutaneous transluminal angioplasty [18]. However, note that the comparability is limited due to low patient numbers. There have been two studies that the combination of tirofiban with unfractionated IV heparin (UFH) or with IV rtPA in the treatment of acute stroke in approach. Junghans et al. have prospectively 18 patients within 24 hours after onset of stroke symptoms included in a study in which they initially with UFH, with a target PTT 50–70 seconds and then tirofiban in the PRISM-PLUS dosage of funds received in 46 hours [19]. Intracerebral hemorrhage is not any way this occurred, however, only a low recanalization rate of 25% will be retained.

Neither tirofiban, heparin still possess thrombolytic properties. The rationale of treatment is rather the time it takes for an endogenous mediated by endothelial cells remains to extend thrombolytic therapy to prevent further thrombus and to prevent reocclusion already re-opened vessels. In addition to the narrow time window that is another problem is that in the sole rTPA administration vessels re-opened in about a third of re-occluded cases [20], which speaks well for it, as in group B of our work in a place lysis treatment, even in terms to follow up re-opened despite the major tribes still limited microcirculation [11], further therapy with a GPIIb/IIIa inhibitors.

Comparing the present data with the results of the already mentioned in the introduction satis study, the only previous completed investigation with tirofiban in a larger cohort of stroke patients, then the long-term outcome in Group A is not as advantageous as for the satis population described. The Barthel Index was in the present study at least three months after stroke on average 71 points (median 90), in Satis-study funds at 1.

Overall, the safety of tirofiban in monotherapy or in combination with various Rekanalisations methods in the treatment of patients with acute ischemic stroke by the present investigation is based. Because of the retrospective, non-controlled study design and the relatively low numbers of patients with heterogeneous treatment approaches, the data must be interpreted with caution, but they give a good insight into the safety of the use of tirofiban in clinical practice.

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