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Original Article

Tirofiban improves rehabilitation therapeutics effects in patients with dyskinesia after stroke

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Abstract: Objectives: Tirofiban is a glycoprotein IIb/IIIa antagonist. Combining Tirofiban treatment with rehabilitation program may have synergistic effect in stroke. The purpose of our research is to determine whether Tirofiban brings about additional repair of motor function in patients at subacute stage of stroke. Methods: Our study was a randomized, multicenter, double-blind, parallel-group, placebo-controlled, prospective study. Sixty-six stroke patients whose motor damage ranged from mild to severe were enrolled in this study. Participants were divided into two groups randomly and went through treatment procedures lasting for 21 days using either placebo or Tirofiban (Tirofibann = 33, placebo n = 33) in addition to standard rehabilitation treatment. Evaluation was conducted at the initial stage of study, as soon as treatment is finished, and 2 months and 3 months subsequent to apoplectic seizure. Results: Patients in both groups had their motor function significantly promoted ($p < 0.05$). Promotion in Tirofiban group was also significantly better than promotion in placebo group ($p < 0.05$). In terms of patients whose motor function was severely damaged, promotion in Tirofiban group was significantly better than promotion in placebo group ($p < 0.01$). Influence of Tirofiban was proved to be limited in gain of diffusivity of corticospinal tract (CST) as well as renewal of sensorimotor network (SMN) connectivity. Conclusions: Our results suggest that Tirofiban in addition to rehabilitation treatment for subacute stroke has high safety and promotes extra repair of motor function in stroke patients whose motor function is seriously damaged.

Keywords: Tirofiban, motor recovery, rehabilitation, stroke, severe motor impairment

Introduction

Stroke occurs when blood supply of brain is obstructed, leading to a severe cerebrovascular event. The insufficiency of blood supply ousts brain cells of oxygen and glucose; bring about malfunction [1]. Stroke ranks second of the most common causes of paralysis all over the world. Even in terms of patients who survive from stroke, 90% of them are accompanied with sequelae [2]. Stroke is the third leading factor to bring about death all over the world, only subsequent to MI and cancer. Not only hemorrhagic but also ischemic stroke is able to attack people of whatever age. There exist some risk factors raising vulnerability to stroke, such as hypertension, smoking, obesity, carotid artery illness, and illness of other arteries [3]. Paralysis in daily activities of patients who survive from stroke mainly results from motor injury [4]. Numerous rehabilitation methods aiming at promotion of motor repair in stroke patients have insufficient influence, especially in patients whose motor injury is serious [5]. Congenital plasticity of anatomy and physiology accounts for the noticeable repair of motor function subsequent to stroke. Overall aerobic exercise additional to training aimed at specific tasks remains gold standard to rehabilitate the patients subsequent to stroke [6]. Subacute stage subsequent to stroke is crucial to recovery because brain cells are the most sensitive to modification after rehabilitation procedures in this period of time.

Tirofiban is the antagonist for IIb/IIIa receptors on platelets without consisting of peptides. It can inhibit aggregation of platelets triggered by diverse substances and eradicate newly produced blood clots, including those consisting of fibrin, so promotes the blood supply to the brain [7]. Consequently, Tirofiban is widely used to endovascular interventional treatment in order to avoid occurrence of thromboembolic

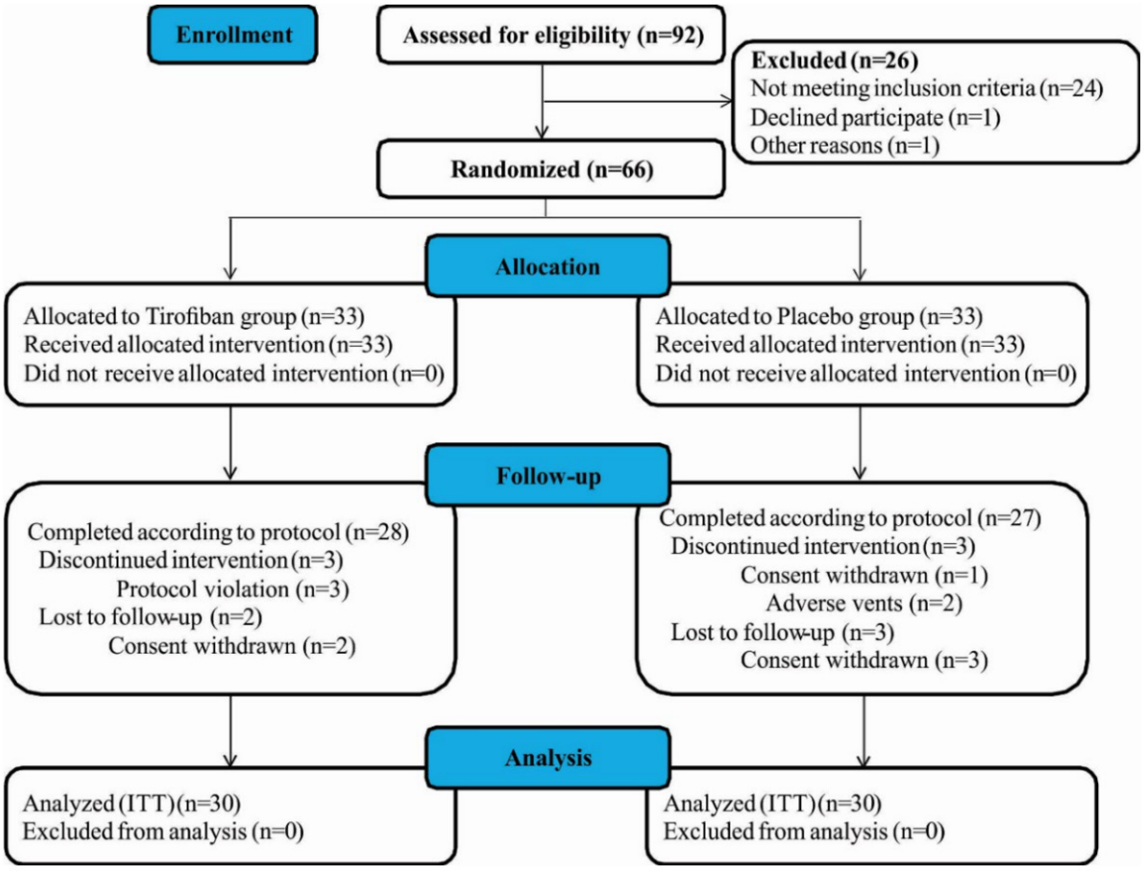

Figure 1. Flow diagram of criteria in the study.

complications triggered by vascular endothelial injury [8]. It has been demonstrated in clinical experiments with large sample size that antagonists for GP IIb/IIIa are efficacious to treat acute coronary syndromes [9]. However, whether Tirofiban brings about additional repair of motor function in patients at subacute stage of stroke remains unclear.

The aim of our research was to estimate Tirofiban's efficacy to additionally improve motor renewal based on rehabilitation procedures in subacute stroke patients whose motor damage ranged from mild to serious. Tirofiban's influence on neuroplasticity has been demonstrated with the help of functional neuroimaging.

Methods

Patient inclusion and exclusion criteria

Affirmed by MRI or CT of brain, patients with primary unilateral cortical-subcortical, subcortical, or cortical infarct were enrolled into our research less than seven days subsequent to apoplectic seizure. The participants were inpatient and their age ranged from 18 to 82. Damage of their motor function ranged from mild to severe (FMA score 0-100) [10]. The criteria for exclusion were listed as follows: unstable or progressive stroke, noticeable drug or alcohol abuse in the prior three years, pre-existing psychiatric or neurological diseases in active stage, terminal cardiac, kidney, liver, or lung illness, terminal disease with predicted OF < 1 year, major disease discovered during randomization with NIHSS score ≥ 2, lactating or pregnant women, history of BNP treatment, participation in other stroke research, cardiopulmonary sequelae affecting physiotherapy, abnormal laboratory results, recent significant surgery, injury, or bleedings [11]. Fully informed consent of every subject was acquired in written form before enrollment. Protocol of our research was approved by People's Hospital of Binhai.

Table 1. Comparsion of Baseline Charateristics

Demographic parameter	Tirofiban (n = 30)	Placebo (n = 30)	*p* value
Male (%)	19 (63.3)	20 (66.7)	0.23
Mean age: years (SD)	59.2 (11.2)	58.7 (12.3)	0.38
Mean weight: kg (SD)	63.2 (10.2)	64.2 (9.9)	0.51
Mean height: cm (SD)	169.2 (7.9)	169.4 (8.2)	0.82
Prevalence of risk factors: N (%)			
Hypertension	15 (50)	16 (53.3)	0.21
Hyperlipidemia	1 (3.33)	2 (6.67)	0.18
Diabetes mellitus	3 (10)	1 (3.33)	0.07
Arrhythmia	0	0	
Coronary artery disease	2 (6.67)	2 (6.67)	0.99
Strok side: N (%)			
R	15 (50)	12 (40)	0.45
L	15 (50)	18 (60)	0.43
Stroke etiology: N (%)			
Large artery atherosclerosis	12 (40)	11 (36.7)	0.55
Small vessel occlusion	12 (40)	13 (43.3)	0.73
Cardioembolism	5 (16.7)	3 (10)	0.08
Other determined	1 (3.33)	1 (3.33)	0.99
Undetermined ischemic stroke	0	2 (6.67)	0.06
Stroke lesion characteristics			
Cortex	4	4	
Cortex/BG/IC	2	2	
Cortex/BG/IC/Corona radiata	1	3	
Cortex/Corona radiata	4	0	
BG/IC	12	14	
BG/IC/Corona radiata	5	4	
Corona radiata	1	2	
Thalamus	1	1	

BG: Basal Ganglia, IC: Internal Capsule.

Treatment method

The design of our research was a multicenter, double-blind, parallel-group, placebo-controlled, prospective, and randomized study. We conducted screening visit less than seven days subsequent to stroke; medical history, characteristic and PE data, and lab experiments were recorded. Participants were randomly divided into two groups and continued to go through treatment procedures lasting for 21 days (Days 8-28) using either placebo or Tirofiban additional to rehabilitation treatment. Tirofiban was intravenously administered at 0.1 g/kg body weight deliquated in saline once a day in no less than 30 minutes in experimental group. Patients in control group only underwent intravenous infusion of saline. Furthermore, every participant went through standard rehabilitation procedures including occupational therapy (OT) for 1 hour as well as physical therapy (PT) for 2 hours from Monday to Friday. Every participant went through a series of passive motion training in their own room instead of overall rehabilitation treatment prior to recruitment. Estimation of safety and efficacy was performed in the initial stage of study (8th day; T0), as soon as the treatment is completed (29th day; T1; endpoint of the study), 2 (60th day; T2) and 3 (90th day; T3) months subsequent to apoplectic seizure. Neuroplasticity alteration of motor network was evaluated with the help of (diffusion tensor imaging) DTI and (resting state functional magnetic resonance imaging) rs-fMRI on T0, T1, and T3. Research period for every participant lasted for ninety days.

Severity of stroke at baseline

Severity of stroke on T0 was documented with the help of NIHSS in terms of every recruited participant. Furthermore, data of structural MRI at T0 were used to evaluate volumes of primary lesion, and then changed into the coordinate frame identical to brain template, in accordance with MNI space utilizing SPM (see http://www.fil.ion.ucl.ac.uk/spm/). The lesion of every participant was depicted manually on standardized structural image and preserved in the form of images of binary mask. Voxels number that make up the mask of lesion was calculated, and multiplied by the voxel size by measuring the volume of the lesion.

Motor function evaluation

In terms of evaluation of motor function, FMA was estimated in the initial stage of study (T0), as soon as the treatment was completed (T1), and two (T2) and three (T3) months subsequent to apoplectic seizure. FMA scores were recorded for the lower limb (FMA-LL), upper limb (FMA-UL), and the total score (FMA-T) separately. FMA is highly valid and credible to

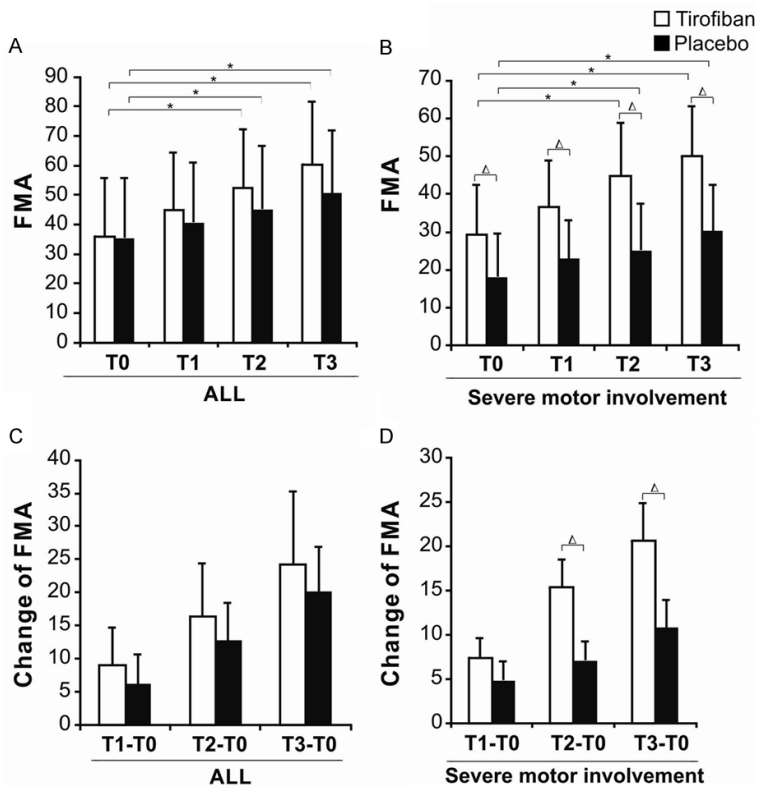

Figure 2. Changes in the FMA for Tirofiban and placebo at T0, T1, T2 and T3 after the onset of stroke. For the ITT population, analysis was performed for the missing data using the LOCF approach, and the subgroup of patients who had severe motor impairment was also analyzed. A. The time course of the total score of FMA for the total population. B. The time course of the total score of FMA for the severe subgroup. C. Improvements from baseline of the total score of FMA for the total population. D. Improvements from baseline of the total score of FMA for the severe subgroup. *, $p < 0.05$ between time points in group. Δ, $p < 0.05$ between both groups.

predict severity of motor injury throughout stroke recovery.

Plasticity evaluation of motor network

Plasticity of motor network was evaluated depending on rsfMRI and DTI imaging data. MR scanner was used to obtain DTI data. Data were processed online (http://fsl.fmrib.ox.ac.uk/fsl/). In terms of every voxel, we produced diffusion tensor. Fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) were calculated by diffusion tensors. In every participant's native space, we changed DTI parameters' maps into MINI space. It was considered an optional method to observe CST of all participants that utilizing template CST acquired from healthy controls was used as a standardized approach to measure corticospinal integrity when using DTI data. For generating the template CST, probabilistic tractography of the CST was performed for age-matched healthy controls. In terms of each participant, AD, RD, and CST-wise fractional anisotropy were calculated in terms of CST within hemisphere on the same side of lesions (ADipsi, RDipsi, and FAipsi).

Data of rsfMRI were acquired with single-shot GE-EPI sequence. Data were preliminarily handled applying routines of SPM (see http://www.fil.ion.ucl.ac.uk/spm/) and DPARSF (http://rfmri.org/DPARSF). In order to evaluate the SMN depending on FC at rest, representative time course (TC) for initial motor cortex (M1) in the hemisphere on the same side of lesions worked as reference to estimate CC with the remaining TC. In terms of every group, SMN was exhibited through setting an SPM of the t value calculated by one-sample t test for SMN of every participant. Additionally, lateralization index (LI) between sensori-motor cortices (SM1s) was calculated. In voxel values more than 95th percentile of map, LI was determined to be distinction of voxel ration between SM1s on the same and opposite side of lesion. Consequently, LIs near zero was defined as symmetrical FC which was presented in SMN of healthy controls.

Safety analyses

Integral PE with vitals and medical history were conducted upon screening. We evaluated lab data on every visit of our research from initial stage of study (T0) to the third month (90th day; T3). All AEs subsequent to notification were recorded and estimated considering mortality and severity.

Statistical analysis

In our research, initial analysis was conducted depending on intention-to treat (ITT) popula-

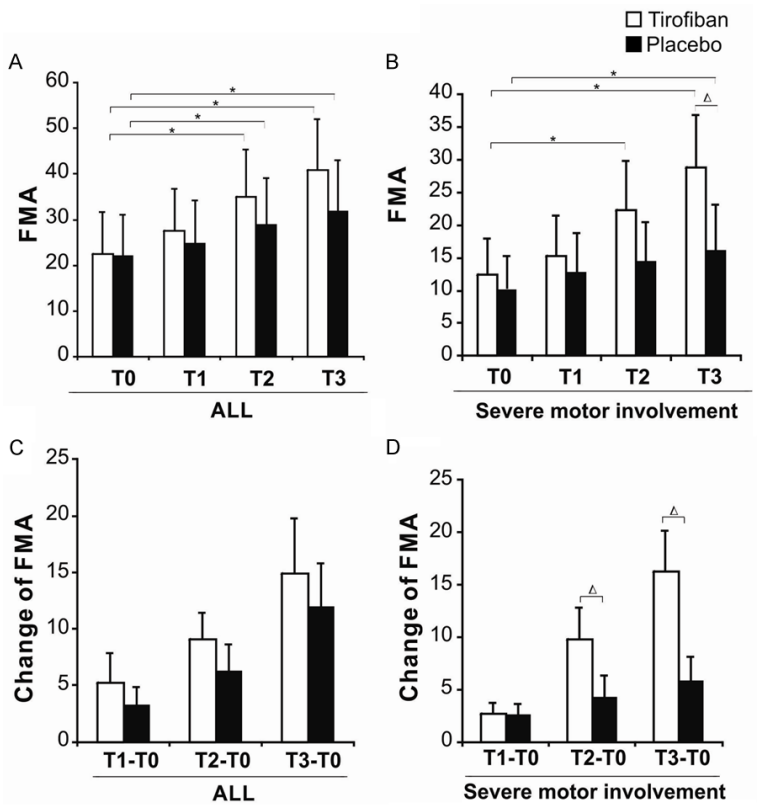

Figure 3. Changes in the FMA for Tirofiban and placebo at T0, T1, T2 and T3 after the onset of stroke. For the ITT population, analysis was performed for the missing data using the LOCF approach, and the subgroup of patients who had severe motor impairment was also analyzed. A. The time course of the upper limb subscore of FMA for the total population. B. Time courses of the upper limb subscore of FMA for the severe subgroup. C. Improvements from baseline of the upper limb subscore of FMA for the total population. D. Improvements from baseline of the upper limb subscore of FMA for the severe subgroup. *, $p < 0.05$ between time points in group. Δ, $p < 0.05$ between both groups.

tion with the help of last observation carried forward (LOCF). ITT population referred to the whole participants who went through no less than one administration of treatment and were estimated in initial stage of study and afterwards at primary endpoint. LOCF substituted missing data with the values last observed. The safety population referred to the whole participants who went through at least one dose of treatment. SPSS 18.0 was applied to statistical analyses. The distinction of the successive results between placebo group and Tirofiban group was evaluated with independent-samples t test. Distinction of frequency was examined with Fisher's exact test or X^2-test. To test the effects of Tirofiban across all time points we used the repeated measures ANOVA with time as the within-patient factor and group (Tirofiban vs. placebo) as the between-patient factor for the parametric data with normal distribution. *P*-value tended to be small if its homologous F-value was large in RM analysis of variance. $P < 0.05$ was regarded as statistically significant.

Results

General data

Sixty-six participants in all were recruited in our research (**Figure 1**). SAP contained all the participants because everyone went through no less than one administration of treatment (Tirofiban *n* = 33, placebo *n* = 33). Eleven participants altogether quitted the research on account of adverse events (AEs) (hemorrhagic transformation (HT); placebo *n* = 2) through retreating consent (Tirofiban *n* = 2, placebo *n* = 3) or due to protocol contravention (Tirofiban *n* = 3). Six participants lacked data subsequent to initial stage of study, and were consequently eliminated from ITT population (Tirofiban *n* = 30, placebo *n* = 30). Males made up 65% of all the participants. Average age of participants turned out to be 58.9 ± 11.7 years. Distinction between groups was not significant in initial stage of research in terms of stroke features (**Table 1**). Considering participants with HT, CAD, occlusion in small vessels, and HL, there was no significant distinction between placebo and Tirofiban group.

Motor function evaluation

In the (ITT-LOCF) analyses, both groups improved significantly over time in the FMA (**Figures 2A**, **3A** and **4A**). Distinction of FMA score promotion between placebo group and Tirofiban group at T3 was not significant (FMA-LL, FMA-UL, and FMA-T). Promotion of FMA score (FMA-UL, FMA-LL, and FMA-T) of Tirofiban

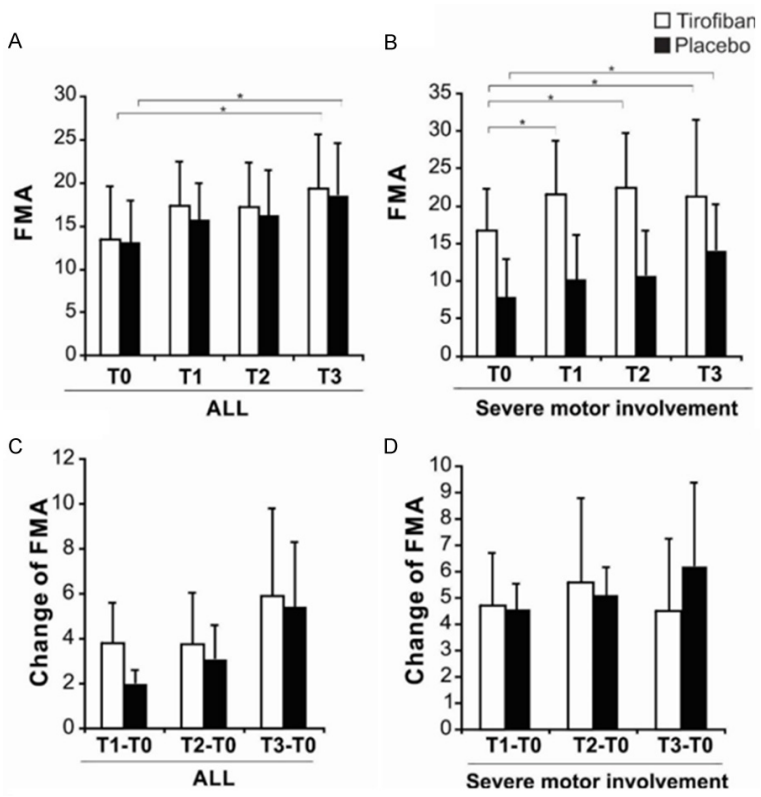

Figure 4. Changes in the FMA for Tirofiban and placebo at T0, T1, T2 and T3 after stroke onset. For the ITT population, analysis was performed for the missing data using the LOCF approach, and the subgroup of patients who had severe motor impairment was also analyzed. A. The time course of the lower limb subscore of FMA for the total population. B. Time courses of the lower limb subscore of FMA for the severe subgroup. C. Improvements from baseline of the lower limb subscoreof FMA for the total population. D. Improvements from baseline of the lower limb subscore of FMA for the severe subgroup. *, $p < 0.05$ between time points in group.

group was mildly stronger than that of placebo group (**Figures 2**-**4**).

In the ITT-LOCF analysis of participants whose motor function was seriously damaged at T0, RM analysis of variance revealed significant interactivity between methods of intervention and time of intervention, which was detected using FMA-UL ($p < 0.05$) (**Figure 3B**) and FMA-T ($p < 0.05$) (**Figure 2B**). Furthermore, group distinction in FMA-UL (**Figure 3D**) and FMA-T (**Figure 2D**) at T3 and T2 was significant, which did not comply with FMA-LL group (**Figure 4**).

Plasticity evaluation of motor network

In diffusion tensor imaging (DTI) analysis of the corticospinal tract according to ITT-LOCF subgroup analysis of participants, who with motor impairment at T0, repeated measures ANOVA showed significant interactions between time and type of intervention for ADipsi ($p < 0.05$, **Figure 5C**) and RDipsi ($p < 0.05$, **Figure 5E**). Furthermore, significant difference was found in the changes among two groups of RDipsi and ADipsi on T3 ($p < 0.05$, **Figure 5D**, **5F**). Nevertheless, in terms of FAipsi, RM analysis of variance revealed that the interactivity between methods of intervention and time of intervention was not significant (**Figure 5A** and **5B**).

Among the participants whose motor function was seriously damaged at T0, data obtained from rsfMRI were examined. As a matter of fact, RM analysis of variance demonstrated that interactivity between methods of intervention and time of intervention was not significant in lateralization index (LI) analysis between sensori-motor cortices (SM1s) on both sides (**Figure 6B**). However, compared with T0, significant difference in LI at T1 and T3 was found only in Tirofiban treatment (**Figure 6A**).

Safety analyses

In terms of the whole participants, 95.6% of them underwent intravenous infusion (placebo 93.2%, Tirofiban 98.4%). One participant from each group developed SAE. Neither of the two serious adverse events (SAE) was proved to be linked with medical care in our research. The SAE of Tirofiban group was cholecystitis triggered by cholelith, which subsided in the period of our experiment. The SAE in the placebo group was a hemorrhagic transformation of the cerebral infarction, the patient discontinued study participation due to this event. No casualty was generated during the whole research. With no clinically related alteration throughout the whole research, lab data and vitals were nearly the same between both groups.

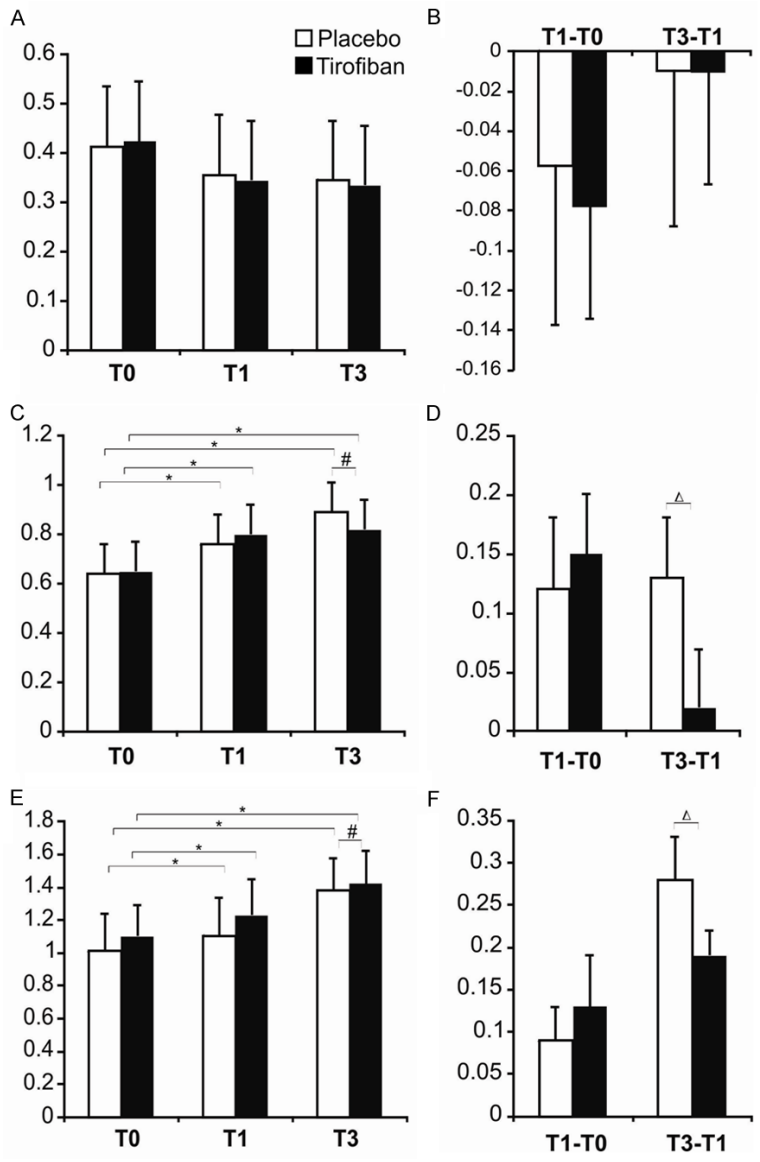

Figure 5. Changes in the DTI for Tirofiban and placebo at T0, T1, T3 after the onset of stroke. The time course (A, C, and E) and the change from baseline (B, D, and F) are provided to the radial diffusivity (RD; E and F), the axial diffusivity (AD; C and D), and the fractional anisotropy (FA; A and B). *, $p < 0.05$ between time points in group. Δ, $p < 0.05$ between both groups. #, $p < 0.05$ between groups over time.

Discussion

Stroke is the main cause bringing about acquired paralysis, and the second most important cause of mortality only inferior to IHD. More than 50% of stroke patients continued to be dependent in physical movement, and almost two in three stroke patients were accompanied with CNS damage 5 years subsequent to stroke [12]. Newly formed or relapsing, stroke was prevalent in 2 million Chinese people, of which approximately 1 million survived but degenerated into secular severe injury in physical movement, language and cognition [13, 14]. As a general complication of stroke, convulsion hindered the spasmodic limbs from normal movement and severely damaged their life quality [15]. Repairment on its own tends to hit plateau from three months to half a year. However, even in plateau period, rehabilitation is efficient to promote physical outcome [16]. Despite the fact that increasing training intensity and time brings about better renewal, conduction of one-on-one training is costly and takes too much time. Consequently, it sparks wide interest in AT to promote recovery [17, 18]. In this study, our findings suggest that Tirofiban in addition to rehabilitation treatment for subacute stroke has high safety and promotes extra repair of motor function in stroke patients whose motor function is seriously damaged.

In this study, we determined whether the three-week treatment of Tirofiban additional to rehabilitation could promote extra motor renewal in stroke patients at subacute stage whose motor function was injured mildly or seriously. It is indicated in recent proof that the early intervening rehabilitation provides remarkable merits to stroke patients [17]. In terms of participants whose motor function was seriously damaged seven days subsequent to apoplectic seizure, Tirofiban combined with rehabilitation significantly promoted extra motor repair three months subsequent to apoplectic seizure. Furthermore, the three-week treatment of Tirofiban in subacute stroke presented no SAEs. Tirofiban additional to rehabili-

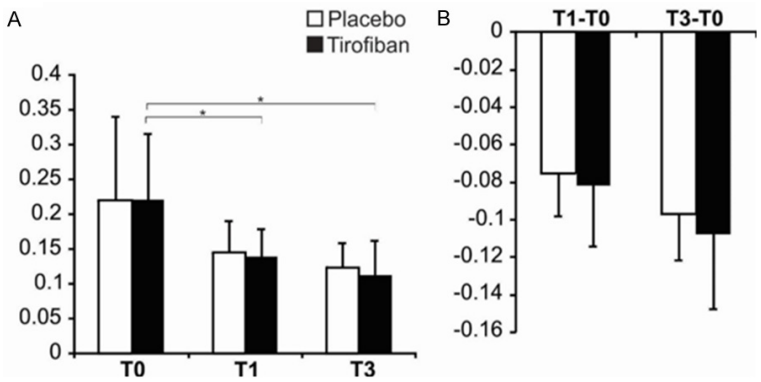

Figure 6. For the ITT population, analysis was performed for the missing data using the LOCF approach in subgroup of patients with severe motor impairment. The time course (A) and the change from baseline (B) are provided to the lateralization index. *, $p < 0.05$ between time points in group.

tation during subacute stroke has been proved to bring about extra motor renewal in participants whose motor function is seriously damaged.

The most adequate time to conduct rehabilitation remains controversial. However, it has been proved that earlier rehabilitation generates better recovery [19, 20]. Actually, therapeutic time window of functional repair is comparatively wide, ranging from a few days to several weeks. Functional repair is defined as promoted motor and sensory performance subsequent to stroke, and may contain diverse compensation in behaviors [21]. Simple repair also utilizes remapping of relevant cortices with the aim of generating novel circuits functionally and structurally [22]. It has been revealed in animal experiments that translation and expression of genes related to plasticity during early development of brain resemble those during subacute stroke [23]. Our research failed to reach primary goal to estimate Tirofiban efficiency of motor repair, but we examined FMA-T promotion from initial stage of study to when the treatment was completed in terms of the participants whose motor damage ranged from mild to serious. Nevertheless, Tirofiban co-treatment with rehabilitation proved more efficient in promotion of seriously damaged motor function three months subsequent to apoplectic seizure in comparison with placebo added to rehabilitation. Diffusibility of the interaction rises over time, which was not so limited or steep in terms of Tirofiban group. RD was proved to be elevated subsequent to motor damage, which represented demyelination. Consequently, constraint of RD elevation in Tirofiban group probably indicates that Tirofiban avoided CST demyelination in subacute stroke. Conversely, AD decline probably is a reflection of injury of axons in acute stage subsequent to stroke, while rise of AD is probably caused by degeneration in chronic stage. Tirofiban has been approved to treat acute coronary syndromes until forty-eight hours subsequent to onset [24]. The impediment of Tirofiban to fibrin-binding receptors in order to avoid aggregation of platelets is efficient and reversible [24]. In SaTIS trial, Tirofiban is proved to be safe in mild acute ischemic stroke [25]. Comprehension by linking the separate pathological process to the directional diffusivity remains under discussion. AD is elevated more steeply in placebo group, suggesting a combination of compensation in structure and degeneration which actually does not produce connections that useful in function. However, FA declined successively till T3 in the group treated with Tirofiban, indicating restore of CS completeness triggered by Tirofiban. The functional connectivity in symmetry of the group treated with Tirofiban was more significant, reflecting a stronger promotion of motor function.

There exist several limitations in our research. First, the distinction between time and intensity of rehabilitation subsequent to treatment procedures (T1) between placebo group and Tirofiban group was not significant. Second, we couldn't modulate the patients for rehabilitation from subsequent to treatment (T1) until three months subsequent to apoplectic seizure (T3), despite the fact that no other brain protecting medication was permitted unless three months subsequent to apoplectic seizure passed by. Third, the comparatively small sample size failed to provide multivariate models in order to modulate for more confounds. Consequently, further research with larger sample size is needed to estimate influence of additional Tirofiban to rehabilitation on motor renewal of subacute stroke patients more con-

vincingly. Fourth, in our research, age and severity of stroke participants were comparatively low, different from other stroke research. This might result from our rigorous exclusion criteria. Fifth, the evaluation of plasticity of the motor network, data acquired from rsfMRI and diffusion tensor imaging were adopted since they have already been widely and reliably utilized to assess motor network in stroke patients. Excessive movements of stroke patients lead rsfRNA to higher vulnerability to artifacts caused by motion.

In summary, this study revealed that a three-week treatment of Tirofiban additional to rehabilitation for subacute stroke not only has high safety but also promotes extra repair of motor function in stroke patients whose motor function is seriously damaged. According to our research, Tirofiban cotreatment with rehabilitation could be regarded as a novel pharmacologic method to promote motor recovery of subacute ischemic stroke patients whose motor function was seriously damaged.

Disclosure of conflict of interest

None.

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