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Effect of tirofiban in treating patients with progressive ischemic stroke

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Abstract. – OBJECTIVE: Our aim is to investigate the efficacy and safety of tirofiban in the treatment of patients experiencing progressive ischemic stroke (PIS).

PATIENTS AND METHODS: A retrospective analysis was performed on the clinical data of 150 patients with ischemic stroke admitted to our hospital from May 2018 to December 2019. All the patients were divided into two groups according to different treatment methods. In Control group, conventional comprehensive treatment and antiplatelet therapy with aspirin + clopidogrel were conducted, while tirofiban was administered in Tirofiban group in addition to the treatments in Control group. Neurological deficits were scored by means of the National Institutes of Health Stroke Scale (NIHSS) at the time of progression and 30 d after treatment, and the modified Rankin Scale (mRS) and Activity of Daily Living (ADL) scale were employed to assess prognosis at 90 d after treatment. Thereafter, the platelet aggregation rate, platelet adhesion rate, plateletcrit (PCT), platelet distribution width (PDW), and platelet inhibition rate were measured before and after treatment. Finally, the patients were followed up, and the occurrence of hemorrhage events during treatment and within 90 d after discharge was recorded.

RESULTS: After treatment, all the patients had significantly lower NIHSS and mRS scores and a dramatically higher Barthel index (BI) than those before treatment ($p<0.001$). At 90 d after treatment, Tirofiban group exhibited significantly higher BI ($p<0.001$) and lower mRS score than Control group ($p=0.011$). In addition, at 14 d after treatment, the clinical efficacy was assessed for all the patients. It was found that the overall response rate in Tirofiban group was substantially higher than that in Control group [82.7% (62/75) *vs.* 64.0% (48/75), $p=0.009$]. At 7 d after treatment, the PCT and adenosine diphosphate (ADP) platelet inhibition rate in Tirofiban group were markedly higher than those in Control group ($p=0.006$, $p<0.001$), and Tirofiban group had remarkably lower measured values of platelet aggregation rate, platelet adhesion rate and PDW than Control group ($p=0.007$, $p=0.021$, $p<0.001$). After treatment, the levels of serum IL-6 and hs-CRP declined notably in the two groups of patients, and the differences in their levels at 2 and 14 d after treatment between the two groups were statistically significant ($p<0.05$). During treatment and within 90 d after discharge, both groups of patients had no cerebral hemorrhage, gastrointestinal hemorrhage, and severe hemorrhage adverse events requiring blood transfusion, but they experienced subcutaneous ecchymosis, epistaxis, gingival hemorrhage, and hemorrhage around the infarct, which were improved after symptomatic treatment. Moreover, the occurrence rate of hemorrhage in Tirofiban group was higher than that in Control group, showing no statistically significant difference ($p>0.05$).

CONCLUSIONS: Tirofiban combined with conventional basic treatment can greatly improve neurological deficits and disease outcomes, alleviate platelet adhesion, and reduce platelet activation without increasing the risk of hemorrhage in PIS patients.

Key Words:
Tirofiban, Ischemic stroke, Progressive, Efficacy.

Introduction

In progressive ischemic stroke (PIS), the symptoms of neurological deficits after the onset of ischemic stroke are mild but gradually aggravated and continue to progress within 48-72 h until severe neurological deficits appear[1]. PIS, accounting for a considerable proportion of ischemic stroke cases, has an occurrence rate of 26-43% and high disability and mortality rates. Currently, there are no reliable and effective treatment methods for PIS[2,3]. Although intravenous thrombolysis is one of the most effective treatments for acute ischemic stroke, it has strict requirements for the selection of treatment time window and is costly, and relevant contraindications need to be excluded[4,5].

Tirofiban, a reversible antagonist of non-peptide platelet glycoprotein (GP) IIb/IIIa receptors, can prevent fibrinogen from binding to GPIIb/IIIa receptors and block the final common pathway of platelet aggregation. Compared with other anti-

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platelet drugs, it is able to inhibit platelet aggregation more thoroughly and potently, and it is assessed to be exactly highly efficacious and safe in acute coronary syndromes and coronary interventions[6,7]. At present, the application of tirofiban in acute ischemic stroke has been explored in some studies, and it is believed that tirofiban quickly inhibits platelet aggregation, dissolves microthrombi, and increases the rate of vascular recanalization[8,9]. This study aims to explore the effects of tirofiban on the neurological function, platelet function and prognosis of patients with PIS, in order to provide a strong basis for the treatment of such patients.

Patients and Methods

Patients

The clinical data of 150 PIS patients admitted to our hospital from May 2018 to December 2019 were collected. All the patients were assigned into two groups according to different treatment methods. Control group received conventional comprehensive treatment and antiplatelet therapy with aspirin + clopidogrel, while tirofiban was administered in Tirofiban group based on the treatments in Control group. Inclusion criteria: patients diagnosed with PIS with reference to the diagnostic criteria in the *Chinese Guidelines on the Diagnosis and Treatment of Acute Ischemic Stroke in 2014*, those experiencing the first onset, those admitted within 24 h after onset, those whose infarct site was confirmed by head computed tomography (CT) and magnetic resonance imaging (MRI) examinations, those receiving no intravenous thrombolysis treatment, those with progressively aggregated symptoms of neurological deficits within 6-72 h after onset, and those with the National Institutes of Health Stroke Scale (NIHSS) score increased by more than 2 points. Exclusion criteria: patients with hemorrhagic infarction or large-area cerebral infarction confirmed by head CT/MRI examinations, those with cerebral infarction caused by cardiogenic cerebral embolism, arterial dissection, Moyamoya or other non-atherosclerosis diseases, those suffering from severe hypertension/hypotension or hyperglycemia/hypoglycemia, those with severe liver or kidney dysfunction, cardiac insufficiency, bleeding diseases, or thrombocytopenia, those who had a recent history of major surgery or arterial puncture, or those with concomitant malignant tumors. Among the 150 patients, 88 were males and 62 were females, aged 39-79 years old, with the mean age of (60.85±9.89) years old. The baseline data of the two groups of patients were not statistically significantly different but comparable (Table I, $p>0.05$). All the enrolled patients were informed of this study according to the Declaration of Helsinki, and they signed the informed consent upon the review by the Ethics Committee of Clinical Medical College of Dali University.

Treatment Methods

Both groups of patients received conventional basic treatment, including conventional oxygen inhalation, dehydration for lowering intracranial pressure, improvement of cerebral circulation, nourishment of nerves, prevention of infection, maintenance of water and electrolyte balance, control of blood pressure and blood glucose, strengthening of lipid-lowering and dual anti-platelet drug therapy (aspirin at 100 mg/d + clopidogrel at 75 mg/d). In Tirofiban group, the patients were treated with tirofiban [Grandpharma (China) Co., Ltd., H20041165] immediately after the symptoms became more severe. Specifically, tirofiban was first administered at a load of 0.4 μg/(kg·min) for 30 min, and then pumped at 0.1 μg/(kg·min) for 3 d using a micropump. The drug administration could be stopped at any time when severe hemorrhage complications occurred. Normal saline was used as placebo in Control group, and its use and treatment duration were the same as those of tirofiban in Tirofiban group. During drug administration, the clinical symptoms were closely observed, and head CT and routine blood and coagulation function testing were conducted again for all the patients 1 week after onset.

Observation Indicators

The NIHSS was used to evaluate the degree of neurological deficits in patients at the time of progression and 2 and 14 d after treatment. Next, the modified Ranking scale (mRS) and the modified Barthel index (BI) of activities of daily living were employed to assess the daily living ability and disease outcomes of patients in both groups at 90 d after treatment. The higher BI score and lower mRS score indicate the stronger ability of the patient to live independently[10,11].

The clinical efficacy was evaluated according to the neurological deficit scoring standard for stroke and divided into complete remission (CR), significant remission (SR), remission, no response (NR) and deterioration. CR: 91-100% reduction in the NIHSS score, SR: 46-90% decrease in the

NIHSS score, remission: 18-45% decline in the NIHSS score, NR: 17% drop in the NIHSS score, and deterioration: an increase in the patient's neurological deficit score. The overall response rate = (number of basic recovery + number of SR + number of remission) / total number of cases × 100%.

Subsequently, the platelet aggregation rate, platelet adhesion rate, plateletcrit (PCT), platelet distribution width (PDW), and platelet inhibition rate were compared between the two groups before treatment and at 7 d after treatment. Fasting blood was sampled before treatment and at 2 and 14 d after treatment, and the changes in the levels of inflammatory factors interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) were compared.

The number of cases of hemorrhage events during treatment and within 90 d after discharge were followed up and recorded. According to the hemorrhage classification standard in the Global Use of Strategies to Open Occluded Coronary Arteries, the hemorrhage was graded as follows: severe bleeding that threatens life, moderate bleeding that requires blood transfusion treatment, and minor bleeding, such as gingival bleeding, nasal bleeding, subcutaneous ecchymosis, other minor bleeding, and bleeding around the infarct.

Statistical Analysis

SPSS 22.0 (IBM, Armonk, NY, USA) software was used for statistical analysis. Measurement data were displayed as mean ± standard deviation ($\overline{\chi}$±s) and comparisons were made between the two groups using *t*-test. Enumeration data were presented as percentage (%), and χ^2-test or Fisher exact probability test was performed for intergroup comparisons. $p<0.05$ was considered to be statistically significant.

Results

Comparison of Scores of Neurological Functions, Disability and Living Ability

There were no statistically significant differences in the NIHSS score, BI and mRS score at the time of progression between the two groups of

Table I. Baseline characteristics of the studied patients.

Parameters	Tirofiban group n=75	Control group n=75	*p*-value
Age (years)	61.88±9.39	60.21±9.73	0.287
Gender (Male/Female)	41/34	47/28	0.407
Mean time since stroke onset (h)	12.43±3.88	11.78±3.93	0.310
Smoking history (n, %)	39 (52.0%)	45 (60.0%)	0.411
Drinking history (n, %)	37 (49.3%)	43 (57.3%)	0.413
Infarction location (n, %)			0.718
Basal ganglia	31 (41.3%)	33 (44.0%)	
Corona radiata	27 (36.0%)	24 (32.0%)	
Cerebellum	12 (16.0%)	14 (18.7%)	
Others	5 (6.7%)	4 (5.3%)	
Infarction type (n, %)			0.604
Large artery atherosclerosis	30 (40.0%)	34 (45.3%)	
Small artery occlusion	32 (42.7%)	29 (38.7%)	
Others	13 (17.3%)	12 (16.0%)	
NIHSS score	6.57±4.27	7.19±4.43	0.384
Systemic diseases (n, %)			
Hypertension	44 (58.7%)	49 (65.3%)	0.400
Diabetes Mellitus	24 (32.0%)	28 (37.3%)	0.493
Coronary heart disease	15 (20.0%)	12 (16.0%)	0.524
Total cholesterol (mmol/L)	5.12±1.02	5.28±1.05	0.345
Low density lipoprotein cholesterin (mmol/L)	3.23±0.75	3.35±0.79	0.342
Triglyceride (mmol/L)	1.22±0.66	1.24±0.72	0.659
Fasting blood-glucose (mmol/L)	6.59±1.58	6.89±1.87	0.290
Creatinine (umol/L)	79.36±23.19	80.74±21.94	0.508
Homocysteine (umol/L)	13.68±5.25	14.57±5.17	0.297

Notes: NIHSS: National Institutes of Health stroke scale.

Table II. Comparison of NIHSS score, Barthel index and mRS scores of patients in the two groups.

Parameters	Tirofiban group n=75	Control group n=75	*p*-value
NIHSS score			
Progression time	10.79±2.47	11.21±2.33	0.286
2 days Posttreatment	7.88±2.35	9.43±2.20	0.001
14 days Posttreatment	5.67±3.61	8.02±3.83	0.001
Barthel index			
Progression time	36.38±8.74	35.50±8.36	0.530
90 days Posttreatment	77.25±9.04	66.24±9.14	0.001
mRS			
Progression time	4.05±0.75	4.14±0.69	0.446
90 days Posttreatment	2.11±1.08	2.58±1.15	0.011

Notes: NIHSS: National Institutes of Health stroke scale; mRS: Modified Rankin scale.

patients ($p>0.05$). After treatment, all the patients had significantly lower NIHSS and mRS score and a dramatically higher BI than those before treatment ($p<0.05$). The NIHSS score in Tirofiban group was considerably lower than that in Control group at 2 and 14 d after treatment ($p<0.001$). Besides, at 90 d after treatment, Tirofiban group had significantly higher BI ($p<0.001$) and lower mRS score than Control group ($p=0.011$). It can be inferred that tirofiban injection can more obviously alleviate neurological deficits and improve the disease outcomes for patients (Table II).

Efficacy in the Two Groups

At 14 d after treatment, the clinical efficacy was evaluated for patients. According to the results, Tirofiban group had 4 (5.3%) cases of CR, 25 (33.3%) cases of SR, 33 (44.0%) cases of remission, 13 (17.3%) cases of NR, and 0 cases of deterioration, and the overall response rate was 82.7% (62/75). In Control group, there were 1 (1.3%) case of CR, 18 (24.0%) cases of SR, 29 (38.7%) cases of remission, 24 (32.0%) cases of NR, and 3 (4.0%) cases of deterioration, and the overall response rate was 64.0% (48/75). The overall response rate in Tirofiban group was substantially higher than that in Control group, showing a statistically significant difference ($p=0.009$) (Table III).

Comparison of Platelet Functions Between the Two Groups of Patients Before and After Treatment

There were no statistically significant differences in the platelet aggregation rate, platelet adhesion rate, PCT, PDW and adenosine diphosphate (ADP) platelet inhibition rate between the two groups before treatment ($p>0.05$). At 7 d after treatment, the PCT and ADP platelet inhibition rate in Tirofiban group were markedly higher than those in Control group ($p=0.006$, $p<0.001$), and Tirofiban group had remarkably lower measured values of platelet aggregation rate, platelet adhesion rate, and PDW than Control group ($p=0.007$, $p=0.021$, $p<0.001$) (Table IV).

Comparison of Serum Inflammatory Factor Expression Levels Between the Two Groups of Patients Before and After Treatment

The differences in the levels of serum IL-6 and hs-CRP between the two groups were not statistically significant at the time of progression ($p=0.649$, $p=0.509$). At 2 d after treat-

Table III. Comparison of clinical efficacy of patients in the two groups.

Parameters	Tirofiban group n=75	Control group n=75	*p*-value
Complete Response	4 (5.3%)	1 (1.3%)	
Significant response	25 (33.3%)	18 (24.0%)	
Response	33 (44.0%)	29 (38.7%)	
No response	13 (17.3%)	24 (32.0%)	
Deterioration	0 (0%)	3 (4.0%)	
ORR (%)	62 (82.7%)	48 (64.0%)	0.009

Notes: ORR: Overall response rate.

Table IV. Comparison of platelet function parameters of patients in the two studied .

Parameters	Tirofiban group n=75	Control group n=75	*p*-value
Platelet aggregation rate (%)			
Pretreatment	34.98±4.35	35.21±5.09	0.665
7 days Posttreatment	28.77±3.58	30.43±3.84	0.007
Platelet adhesion rate (%)			
Pretreatment	44.93±3.11	44.25±4.03	0.249
7 days Posttreatment	34.81±3.47	36.06±3.05	0.021
PCT (Thrombocytocrit) (%)			
Pretreatment	0.25±0.06	0.26±0.07	0.349
7 days Posttreatment	0.35±0.07	0.32±0.06	0.006
Platelet Distribution Width (fl)			
Pretreatment	16.55±1.24	16.33±1.25	0.281
7 days Posttreatment	12.04±1.49	13.79±1.36	0.001
ADP Platelet inhibition rate (%)			
Pretreatment	32.23±4.20	32.96±5.64	0.370
7 days Posttreatment	46.42±7.10	43.21±7.27	0.001

Notes: ADP: Adenosine diphosphate.

ment, the level of serum IL-6 declined from (123.70±25.88) pg/mL to (98.64±19.75) pg/mL in Tirofiban group and from (125.13±26.54) pg/mL to (107.31±19.91) pg/mL in Control group, and the level of serum hs-CRP was decreased from (4.19±1.09) mg/L and (4.31±1.13) mg/L to (2.92±1.04) mg/L and (3.30±1.22) mg/L, respectively, in Tirofiban group and Control group. The differences between the two groups were statistically significant (p=0.008, p=0.042). At 14 d after treatment, the level of serum IL-6 declined to (79.57±14.69) pg/mL, and (90.40±15.46) pg/mL, respectively, in Tirofiban group and Control group, and the level of hs-CRP was decreased to (2.16±0.92) mg/L and (2.77±0.87) mg/L, respectively, displaying statistically significant differences (p<0.001) (Figure 1).

Comparison of Occurrence of Treatment-Related Hemorrhage Adverse Events Between the Two Groups of Patients

Both groups of patients suffered from no cerebral hemorrhage, gastrointestinal hemorrhage or severe hemorrhage adverse event requiring blood transfusion during treatment and within 90 d after discharge. The occurrence rates of subcutaneous ecchymosis were 6.7% and 4.0%, respectively, those of epistaxis were 2.7% and 0%, respectively, those of gingival hemorrhage were 5.3% and 2.7%, respectively, and those of hemorrhage around the infarct were 10.7% and 5.3%, respectively, in Tirofiban group and Control group. Furthermore, tirofiban group had a higher occurrence rate of hemorrhage events than Control group, but the difference was not statistically significant, indicating that Tirofiban injection did not increase the hemorrhage risk of patients during treatment (p>0.05) (Table V).

Discussion

PIS, a special type of ischemic stroke, is characterized by progressively worsened symptoms of neurological deficits, deterioration within 48 h, and poor prognosis in patients. The pathogenesis of PIS is relatively complex, and progression of thrombosis is one of the main pathogeneses. Thrombosis is related to abnormal platelet activation, adhesion, and aggregation, and activat-

Table V. Comparison of bleeding events incidence of patients in the two groups.

Parameters	Tirofiban group n=75	Control group n=75	*p*-value
Ecchymosis	5 (6.7%)	3 (4.0%)	0.467
Epistaxis	2 (2.7%)	0 (0%)	0.155
Gingival hemorrhage	4 (5.3%)	2 (2.7%)	0.405
Hemorrhage around the infarction	8 (10.7%)	4 (5.3%)	0.229

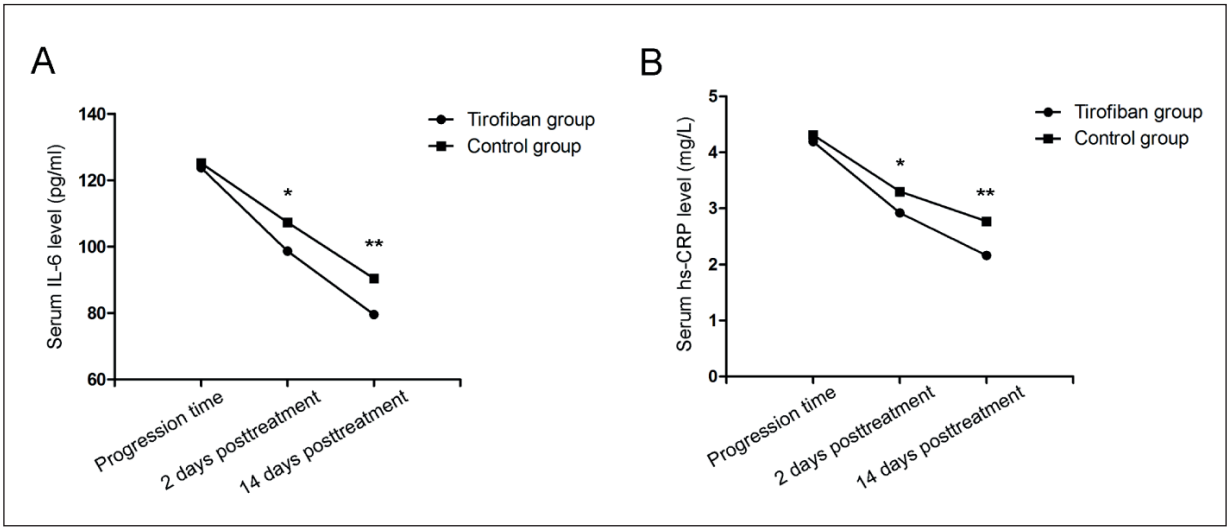

Figure 1. Comparison of serum IL-6 (**A**), hs-CRP (**B**) levels at progression time and after treatment of the studied patients. The difference between serum IL-6 (**A**), hs-CRP (**B**) levels at progression time of patients in Tirofiban group and Control group had no statistical significance ($p>0.05$). Serum IL-6 (**A**), hs-CRP (**B**) levels of patients were significantly decreased after treatment ($p<0.05$). 2 days posttreatment serum IL-6 (**A**), hs-CRP (**B**) levels of patients in Tirofiban group were significantly lower than those of Control group ($p=0.008$, $p=0.042$). 14 days posttreatment serum IL-6 (**A**), hs-CRP (**B**) levels of patients in Tirofiban group were significantly lower than those of Control group ($p<0.001$). *$p<0.05$, ** $p<0.01$.

ed platelets are involved in the occurrence and progression of cerebral ischemic injury[12]. Since thrombolytic therapy has a certain treatment time window and is restricted by contraindications, medical equipment and treatment costs, the current clinical treatment of PIS is mainly anticoagulation and antiplatelet therapies[13].

Tirofiban is a non-peptide platelet GPIIb/IIIa receptor antagonist that can prevent the binding of fibrinogen to GPIIb/IIIa. It is characterized by a short half-life (t1/2=2 h), fast metabolism, and few side effects. Moreover, it can specifically and quickly inhibit platelet aggregation and inhibit the ultimate key target of platelet aggregation and can be widely used in acute coronary syndrome and after coronary stent implantation, producing significant efficacy[14,15]. In a study of the clinical efficacy of tirofiban, 25 patients with acute ischemic stroke who were intravenously administered with tirofiban were compared with those treated with aspirin and clopidogrel as control group. The results showed that tirofiban group had a lower NIHSS score at 7 d after treatment, and a higher mRS score at 90 d after treatment than aspirin group, indicating that tirofiban is more efficacious[16]. The studies on the efficacy of tirofiban in treating SIP have been reported. For example, Martin-Schild et al[17] intravenously administered tirofiban to 24 patients with subcortical infarction within the first 12 h of stroke progression. Among them, 42% had an exercise score less than or equal to the score before symptom exacerbation in the NIHSS score after the application of tirofiban. This manifests that GPIIb/IIIa inhibitors are quite effective in interfering with progression of stroke.

According to the results in this study, the NIHSS score in Tirofiban group was considerably lower than that in Control group at 2 and 14 d after treatment ($p<0.001$). At 90 d after treatment, Tirofiban group had significantly higher BI ($p<0.001$) and mRS score ($p=0.011$) than Control group. It can be inferred that tirofiban injection can more obviously alleviate neurological deficits and improve the disease prognosis for patients. At 14 d after treatment, the overall response rate in Tirofiban group was significantly higher than that in Control group (82.7% *vs.* 64.0%, $p=0.009$), implying that tirofiban injection is more efficacious than aspirin in the treatment of PIS, and can better improve neurological deficits.

Abnormal activation of platelets is one of the major causes of thrombosis. Platelet aggregation and platelet adhesion rates are commonly used clinical indicators for platelet activity. PCT reflects the number and volume of platelets, while PDW, an index of platelet volume variation in the blood, represents the uniformity of platelet volume. The higher the levels of PCT and PDW, the more likely platelet aggregation and adhesion are to occur[18]. Thromboxane A2, a product of AA, can

induce platelet aggregation, while ADP binds to platelet surface receptors to mediate the activation of fibrinogen and GP complexes, inducing platelet aggregation as well[19]. In the present study, the measured values of PCT and ADP platelet inhibition rate at 7 d after treatment in Tirofiban group were notably higher than those in Control group, but the measured values of platelet aggregation rate, platelet adhesion rate, and PDW were considerably lower than those in Control group.

Studies have demonstrated that the detection of hs-CRP can be used to evaluate the overall clinical effect against cerebrovascular diseases, so it has become a possible predictor of the clinical efficacy against cerebrovascular diseases. Chen et al[20] and Di Napoli et al[21] illustrated that the level of hs-CRP at admission can be used to predict the recurrence of stroke in the future compared with that before stroke, and it is obviously positively correlated with the severity of stroke. Vila et al[22] found that the patients with a higher level of IL-6 suffered from more severe neurological deficits, and IL-6 levels peaked at about 3 d, suggesting that IL-6 level is closely correlated with the severity of stroke and poor prognosis. Consistent with the above results, the results of this study showed that tirofiban injection reduced the inflammatory factor IL-6 more remarkably, and IL-6 was related to the severity of neurological deficits.

During treatment and within 90 d after discharge, both groups of patients had no cerebral hemorrhage, gastrointestinal hemorrhage, and severe hemorrhage adverse events requiring blood transfusion. Tirofiban group had a higher occurrence rate of hemorrhage events than Control group, showing no statistically significant difference. In an open study, Junghans et al[23] compared 18 patients with progressively worsening acute ischemic stroke who received weight-adjusted intravenous infusion with 17 controls with acute ischemic stroke and found that none of the patients in both groups had massive intracranial hemorrhage. In line with the results of this study, this shows that tirofiban injection does not increase the risk of hemorrhage in patients during treatment, and it is safer.

This study was a retrospective study with a limited number of patients enrolled, relatively short follow-up time, and incomprehensive follow-up content. Besides, the long-term prognosis of patients was not analyzed. In the future, large-sample, multi-center long-term follow-up studies will be needed to verify the conclusion of this study.

Conclusions

Tirofiban combined with conventional basic treatment can greatly improve neurological deficits and disease outcomes, alleviate platelet adhesion, and reduce platelet activation without increasing the risk of hemorrhage in PIS patients, thus providing a potential strategy for the treatment of progressive ischemic stroke.

Conflict of Interests

The authors declare that they have no conflict of interest.

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