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Clinical study of tirofiban compared to low molecular weight heparin in the antithrombotic treatment of progressive pontine infarction

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Abstract. – OBJECTIVE: To investigate the efficacy and safety of tirofiban and low molecular weight heparin (LMWH) in the treatment of patients undergoing acute progressive pontine infarction.

PATIENTS AND METHODS: Patients with acute progressive pontine infarction who were hospitalized in the Neurology Department from June 2021 to June 2023 were included in the study and randomly divided into two groups, namely the experimental group (tirofiban group) and the control group (LMWH group). All patients in both groups were required to receive conventional comprehensive treatment and dual antiplatelet therapy with aspirin + clopidogrel at the beginning of admission. The National Institutes of Health Stroke Scale (NIHSS) score and Barthel Index (BI) were used to evaluate the neurological deficits on the first day of admission, the next day with stroke progression, and at discharge after treatment with tirofiban and LMWH, respectively in the two groups. The modified Rankin Scale was employed to assess prognosis on the 90th day after treatment. Clinical adverse events were followed up for 90 days, comparing the clinical efficacy and safety of the two treatment methods.

RESULTS: There was no statistical significance in NIHSS score and Barthel Index between the tirofiban group and the LMWH group on the first day of admission and the next day with stroke progression ($p > 0.05$). After stroke progression, tirofiban and LMWH were separately used for treatment in the two groups. We found that the NIHSS score of the tirofiban group was lower than that of the LMWH group, and the Barthel Index score was higher than that of the LMWH group at discharge ($p < 0.05$). After three months of follow-up, the mRS score of the tirofiban group was dramatically higher than that of the LMWH group ($p < 0.05$). No significant harmful or adverse reactions, such as bleeding events, were found in the two groups ($p > 0.05$).

CONCLUSIONS: Tirofiban may be more effective and safer than LMWH in controlling the progression of acute pontine infarction, but further and large-sample studies are still needed to confirm this finding.

Key Words:
Tirofiban, Low molecular weight heparin, Progressive pontine infarction, Neurological deficit,

Introduction

Progressive stroke is a common clinical stroke subtype of acute cerebral infarction. The incidence rate accounts for approximately 29% to 37% of acute cerebral infarction[1]. It is characterized by high disability, mortality and recurrence rate, making it impossible to treat[2-4]. However, pontine infarction is more commonly observed in progressive stroke, leading to a higher likelihood of progression and long-term neurological deficits. At present, emergency intravenous thrombolysis within 4.5 hours of symptom onset and arterial bridging thrombectomy are the most effective interventions for acute ischemic stroke[3]. However, there are currently no particularly effective methods for patients who have missed the opportunity for thrombolysis and are still progressing with conventional treatment. Some studies[5] have reported that low molecular weight heparin can improve collateral circulation, salvage ischemic penumbra, and alleviate neurological deficits, and it has been widely used in the clinical treatment of cerebral infarction, especially in patients with posterior circulation infarction. However, in recent years, research on the application of a new antiplatelet drug, tirofiban, in the clinical treatment of acute progressive cerebral infarction has gradually increased. This article mainly investigates the efficacy and safety of tirofiban and low molecular weight heparin in the treatment of patients with progressive pontine infarction.

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Patients and Methods

Patients

From June 2021 to June 2023, 90 patients who were continuously hospitalized with progressive pontine infarction were included in the study and divided into an experimental group and a control group using a random number table, with 45 cases in each group. In the experimental group, there were 28 males and 17 females, aged 45 to 73, with an average of 61.83 ± 2.32 years old. There were 35 cases of hypertension, 38 cases of hyperlipidemia, 32 cases of diabetes, and 23 smokers etc. In the control group, there were 25 males and 20 females, aged 42 to 72, with an average of 60.43 ± 1.99 years old. There were 33 cases of hypertension, 34 cases of hyperlipidemia, 37 cases of diabetes, and 22 smokers etc.

Inclusion Criteria

(1) 18 years ≤ Age ≤ 75 years; (2) Patients who met the diagnostic criteria for acute pontine infarction in the 2018 Chinese Guidelines for Ischemic Cerebral Infarction, accompanied by varying degrees of neurological deficits and progressively worsening symptoms: within seven days of admission, the maximum NIHSS score increases by ≥ 2 points from the initial value or by ≥ 1 point in exercise. All patients underwent brain magnetic resonance imaging (MRI, including DWI) and computed tomography angiography (CTA). (3) Patients who refused to undergo intravascular thrombolysis or endovascular treatment or miss the thrombolytic therapeutic time window. (4) 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 Ruian People's Hospital.

Exclusion Criteria

(1) Patients allergic to the experimental drug; (2) Patients with mental disorders; (3) Patients who recently had a history of severe trauma or major surgery; (4) Patients with severe comorbidities, such as tumors, acute heart failure, liver and kidney failure, etc; (5) Platelet count less than 100×10^9/l; (6) Patients with cardiogenic stroke triggers such as atrial fibrillation and sick sinus syndrome.

Treatment Methods

On the day of admission, all the enrolled patients had been routinely administrated with aspirin [Bayer Healthcare (China) Co., Ltd., H20171021] 100 mg and clopidogrel [Sanofi (Hangzhou, China) Pharmaceutical Co., Ltd., J20180029] 300 mg. The next day after admission, the patients' condition was aggravated, and dual-antiplatelet therapy was stopped. The patients were randomly divided into an experimental group, which received tirofiban [Grandpharma (China) Co., Ltd., H20041165] therapy (intravenous micro-pump injection, initial dose of 0.4 μg/kg•min, 30 minutes later, at the speed of 0.1 μg/kg•min, continuous application time ≤ 72 hours) and control group, which received the therapy of LMWH (5 days of LMWH treatment, 85-100 IU/kg, once every 12 hours or different doses selected based on body weight). When the two therapeutic methods were accomplished, the treatment plan was adjusted to conventional dual-antiplatelet therapy, with aspirin 100 mg+clopidogrel 75 mg (3 weeks for small artery lesions, then followed by aspirin 100 mg or clopidogrel 75 mg antiplatelet therapy alone; 3 months for large atherosclerosis lesions).

Observation Indicators

NIHSS score and Barthel Index were assessed on the day of admission, the day after progression, and at discharge. A modified Rankin Scale (mRS) score was conducted to assess the clinical prognosis at 90 days follow-up after discharge. The higher BI score and lower mRS score indicated the stronger ability of the patient to live independently. The main adverse reactions were observed and recorded after treatment in both groups, such as intracranial hemorrhage, gastrointestinal bleeding, urinary tract bleeding, and oral bleeding.

Statistics Analysis

All categorical variables are summarized as numbers and frequency (%), and the Chi-squared test or Fisher's exact test was conducted to detect differences between groups. For continuous variables, mean with standard deviation (SD) or median with interquartile range (IQR) are presented to summarize data, and between-group comparisons were performed via independent samples 2-tailed *t*-test or Mann-Whitney U test. Statistical analyses were processed and executed by SPSS 27.0 (IBM Corp., Armonk, NY, USA) with a significance level of $p < 0.05$.

Results

Comparison of Baseline Characteristics Between the Two Groups

The baseline characteristics of the two groups were not statistically significantly different but comparable (Table I, $p > 0.05$).

Table I. Baseline characteristics between the two groups.

Parameters	Tirofiban group	LMWH group	*p*-value
Age (years)	61.83 ± 2.32	60.43 ± 1.99	0.455
Gender (Male/Female, n, %)	28 (62.22%)	25 (55.56%)	0.520
	17 (37.78%)	20 (44.44%)	
Weight	63.00 ± 1.71	63.34 ± 1.57	0.702
Height	165.52 ± 1.73	163.98 ± 1.78	0.196
Hypertension, (n, %)	35 (77.78%)	33 (73.33%)	0.624
Hyperlipidemia, (n, %)	38 (84.44%)	34 (75.56%)	0.292
Diabetes Mellitus, (n, %)	32 (71.11%)	37 (82.22%)	0.213
Smoking, (n, %)	23 (51.11%)	22 (48.89%)	0.833
Platelet count	171.15 ± 9.38	184.65 ± 13.67	0.220

Low molecular weight heparin (LMWH).

Comparison of NIHSS Score, Barthel Index and mRS Scores Between the Two Groups

Before the drug intervention, the differences in the NIHSS scores and Barthel Index of the two groups were not statistically significant ($p > 0.05$). After treatment, the NIHSS score of the experimental group was lower than that of the control group, and the Barthel Index was higher than that of the control group. The difference was statistically significant ($p < 0.05$). The proportion of patients with mRS scores < 3 in the experimental group after three months of follow-up was 82.22%, significantly higher than the control group's 55.56% ($p < 0.05$). Therefore, we could infer that the application of tirofiban more evidently alleviated neurological deficits and improved the disease outcomes for patients (Table II).

Comparison of Occurrence of Adverse Events Between the Two Groups

Both groups of patients did not experience serious adverse reactions, such as cerebral hemorrhage, gastrointestinal hemorrhage, urinary tract bleeding, oral bleeding or events that required blood transfusion during treatment and within 90 days after treatment, confirming a very high level of safety, as shown in Table III ($p > 0.05$).

Discussion

Pontine infarction is the most common type of posterior circulation infarction[4], which has a complex anatomical structure, diverse stroke symptoms and signs, and is difficult to diagnose and treat in early clinical practice. Progressive cerebral stroke currently lacks a clear definition[6], with a higher disability rate and mortality rate than those of non-progressive cerebral stroke, and most patients have varying degrees of neurological deficit symptoms[7,8]. By the time medical attention is sought, the window for thrombolysis has passed, hindering the recovery of daily abilities. Currently, it is believed that the main cause of progressive pontine infarction is atherosclerotic changes in the vertebral-basilar artery and its

Table II. Comparison of NIHSS score, Barthel Index and mRS scores between the two groups.

Parameters	Tirofiban group	LMWH group	*p*-value
NIHSS score			
Admission	3.26 ± 0.22	3.28 ± 0.20	0.796
Progression	7.06 ± 0.24	7.30 ± 0.18	0.079
Discharge	2.39 ± 0.18	5.39 ± 0.19	< 0.001[a]
Barthel Index			
Admission	67.12 ± 3.89	66.86 ± 3.59	0.886
Progression	33.05 ± 2.34	32.78 ± 2.24	0.895
Discharge	82.78 ± 2.02	52.10 ± 2.16	< 0.001[b]
mRS score			
< 3	37 (82.22%)	25 (55.56%)	1.000[c]
> 3	8 (17.78%)	20 (44.44%)	

Compared with the control group, [a,b]$p < 0.05$; [c]$p > 0.05$. Low molecular weight heparin (LMWH), National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS).

Table III. Comparison of occurrence of adverse events between the two groups.

Parameters	Tirofiban group	LMWH group	*p*-value
Adverse reaction			
Intracranial hemorrhage	0	0	
Gastrointestinal bleeding	0	1	
Urinary tract bleeding	0	1	
Oral bleeding	1	0	
Adverse reaction incidence	4.44%	6.67%	0.645[d]

Compared with the control group, [d]$p > 0.05$. Low molecular weight heparin (LMWH).

branches. Research by Yamamoto et al[9] suggests that there are three pathogenesis mechanisms of pontine infarction: (1) Atherosclerotic plaques occur at the origin of the perforating arteries derived from the basal artery, and unstable plaques cause secondary hemorrhage accompanied by thrombus formation[10]; (2) Ischemia of perforating arteries caused by the main lesion of the basal artery, leading to infarction when compensation is insufficient; (3) Formation of atherosclerotic plaques at the junction of the basal artery and perforating arteries. Therefore, based on different pathogenesis mechanisms, domestic and foreign research divides pontine infarction into three different types, namely large-artery occlusive disease (LAOD), basilar artery branching disease (BABD), and small artery disease (SAD). Among them, BABD is more common in clinical practice, with about 60% of pontine infarctions being pontine perforating disease, also known as paramedian pontine artery infarction[11], which is more likely to fluctuate and worsen.

Pontine infarction often has atypical clinical symptoms, and patients may only show dizziness or vertigo, nausea, vomiting, and instability while walking, which are easily overlooked in the early stage. And it is very likely to develop stroke progression[12]. At present, it is believed that stroke progression is mainly caused by platelet activation or the formation of platelet-coagulation fibrin clots secondary to thrombosis. Clinically, it is found that about 80% of the patients have missed the best clinical treatment time when they come for treatment, and at this time, they often adopt drug treatment plans such as strengthening antiplatelet, strengthening statin, scavenging free radicals, combining anticoagulation or fluid resuscitation. A number of studies by Sun et al[5] in China have proposed that the single use of aspirin or clopidogrel combined with low molecular weight heparin to treat progressive cerebral stroke can significantly improve the early neurological deterioration (END) of patients and the clinical efficacy is better than the dual antiplatelet treatment of aspirin and clopidogrel. However, there are also studies with similarly different views. For example, Takeda et al[13] found that the combination of anticoagulant and antiplatelet drugs cannot prevent the progression of acute symptoms but is beneficial to improving the prognosis of patients. Therefore, the combined drug treatment of progressive stroke is currently widely adopted[14-16].

Low molecular weight heparin is prepared by depolymerization of ordinary heparin; it has anti-factor Xa, is anticoagulant, promotes fibrinolytic and increasing endothelial cell antithrombotic ability[17,18], and has been widely used in the treatment of cerebral infarction, especially posterior circulation infarction. Some studies[19] have shown that low molecular weight heparin can increase blood perfusion, reduce the area of cerebral infarction, and thus alleviate ischemia of infarcted brain tissue. However, tirofiban, as a new type of antiplatelet drug, has been widely used in the treatment of heart diseases such as coronary heart disease[20], and its application in ischemic cerebrovascular disease has become a research hotspot in recent years. It is a small molecule non-peptide tyrosine derivative, has selective competitive inhibition of glycoprotein IIb/IIIa receptors, has a significant dose dependence, and can effectively block the chain reaction of platelet aggregation. The drug takes effect quickly and has an antiplatelet aggregation effect within 5 min after intravenous injection. The drug's peak time is < 30 min and the drug's half-life is short, thus reducing the risk of bleeding[21]; compared with low molecular weight, heparin is a better choice. Some studies[22,23] have found that, on the basis of routine cerebral infarction treatment, the use of tirofiban is better than low molecular weight heparin, with similar safety. For acute cerebral infarction patients who have not undergone intravenous

thrombolysis because of the exceeding time window, tirofiban can effectively reduce neurological deficits and improve daily living ability. Similarly, research by Liu et al[24] believes that, whether it is large artery atherosclerosis or perforating artery disease leading to acute progressive cerebral infarction, tirofiban has a good effect and does not increase the risk of bleeding.

Limitations

However, some potential limitations need to be considered in this study. First, it has a small sample size. Second, it is a single-center study with a short follow-up time. Therefore, subsequent large-sample randomized controlled studies or cooperation with multiple centers are still needed. In summary, it is important to seek the best treatment options for different types of infarction.

Conclusions

This study is based on the CHANCE research guidelines established by Professor Wang Yongjun[25], and it is found that the use of tirofiban treatment based on routine dual anti-treatment can more effectively inhibit platelet aggregation, prevent thrombus formation, and promote patient's neurological function recovery, which is a good choice for some patients who missed early treatment[26]. Tirofiban has a strong antiplatelet aggregation effect, and it is hoped that it will have a more prominent performance in the treatment of acute cerebral infarction in the future.

Informed Consent

Informed consent was obtained from all subjects involved in the study.

Ethics Approval

This study was conducted in accordance with the ethical regulations of the Declaration of Helsinki. The experiment has been approved by the Ethics Committee of the Third Affiliated Hospital of Wenzhou Medical University (approval number: YJ2024022; approval date: February 15, 2024).

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Conflict of Interest

The authors declare that they have no conflict of interest.

Authors' Contributions

Q. Zhou edited the manuscript and performed the experiment. L.-E. Xu and L.-L. Lin collected data. X.-R. Huang, W.-Z. Chi, and J. Lin processed the data and the statistics. Q. Zhou and P. Lin designed the research, provided critical comments, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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