Tropical Journal of Pharmaceutical Research September 2023; 22 (9): 1975-1981
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v22i9.28

Original Research Article

Safety and efficacy of arterial injection of tirofiban in treating ischemic stroke beyond the window period

Qiongwen Rong[1,2], Fenglei Chen[1,2], Yuanyuan Ma[1,2]*, Yi Cai[1,2]
[1]Department of Neurology, The First Affiliated Hospital of Hainan Medical University, Haikou 570102, [2]The First Clinical Medicine College, Hainan Medical University, Haikou 571199, China

For correspondence:* ***Email:* *mayuanyuan@hainmc.edu.cn;* ***Tel:*** *+86-089866528133*

Sent for review: 11 April 2023 *Revised accepted: 28 August 2023*

Abstract

Purpose: *To investigate the efficacy of intraarterial administration of tirofiban for stroke treatment beyond the conventional window period and evaluate its impact on prognosis.*
Methods: *A retrospective study was conducted on ninety (90) acute ischemic stroke patients admitted to The First Affiliated Hospital of Hainan Medical University, Haikou, China from July 2021 to October 2022. The patients were divided into Tirofiban group (50) and non-Tirofiban group (40) based on whether the patients received arterial clopidogrel. National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS) and Barthel index (BI) scores were used to evaluate adverse drug reactions and its impact on prognosis for patients with symptoms onset within 6 - 24 h.*
Results: *No significant differences were observed between the groups in terms of age, gender, medical history, personal history, blood indicators and neurologic function scores ($p > 0.05$). The median NIHSS score on admission and after 24 h of treatment was 4 in both groups and 3 in both groups after 72 h of treatment. However, after 7 days of treatment, the median NIHSS score was lower in Tirofiban group (2.0) than in non-Tirofiban group (2.5; $p > 0.05$). Tirofiban group demonstrated higher rates of effective treatment and good prognosis compared to non-Tirofiban group. Importantly, there was no significant difference in the occurrence of adverse reactions between the two groups ($p > 0.05$).*
Conclusion: *Tirofiban, given via the arteries, improves neurological functions following hyper-acute stroke even beyond the window period and without adverse reactions. It is a safe and effective antiplatelet drug for late-life treatment. For future studies, it will be necessary to broaden the treatment scope and gather more robust and reliable data in order to enhance data quality.*

Keywords: *Cerebral infarction beyond time window, Tirofiban, Arterial injection*

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INTRODUCTION

Stroke is a disease with a high incidence, disability rate and mortality rate worldwide [1]. With aging, the prevalence of stroke in patients is projected to exhibit a progressive increase, necessitating the development of superior therapeutic interventions to enhance stroke treatment outcomes [2]. Administration of intravenous recombinant tissue plasminogen activator (rt-PA) within 4.5 hours of symptom onset, coupled with timely implementation of vascular intervention therapy (mechanical thrombectomy) within 6 hours of onset, has been

demonstrated to effectively ameliorate neurological deficits in patients with acute ischemic stroke [3]. However, for patients outside the thrombolytic time window, there is currently no better treatment option. Studies have shown that tirofiban is an effective treatment for acute ischemic stroke and it is beneficial for the recovery of neurological function [4].

For patients with acute ischemic stroke outside the thrombolytic time window, the administration of intravenous tirofiban has demonstrated efficacy in ameliorating neurological deficit symptoms in patients, while maintaining a favorable risk profile without an associated increase in bleeding complications [5,6]. Even during vascular intervention therapy, arterial injection of tirofiban seems to be safer and more effective than without tirofiban [7]. In order to further determine the safety and efficacy of arterial injection of tirofiban for patients with acute ischemic stroke outside the thrombolytic time window, a retrospective analysis was conducted of acute ischemic stroke patients who were treated within 6 - 24 hours of onset and underwent whole-brain vascular imaging. To evaluate the effectiveness of tirofiban, the patients were categorized into two groups: Tirofiban group, comprising individuals who received arterial injection of tirofiban, and non-Tirofiban group, composed of patients who did not receive tirofiban treatment.

METHODS

Patients

Ninety (90) patients with acute ischemic stroke caused by small vessel occlusion and admitted to the Neurology Department of The First Affiliated Hospital of Hainan Medical University, Haikou, China from July 2021 to October 2022, were retrospectively selected. The onset of stroke occurred within 6 - 24 hours before admission and was confirmed via whole-brain vascular imaging. This study was approved by the Ethics Committee of The First Affiliated Hospital of Hainan Medical University (approval no. 20 – HMU – 201), and complied with international guidelines for human studies. Written and signed informed consent was obtained from all participants before the study.

Inclusion criteria

The following specific inclusion criteria ensured the selection of eligible patients for the study. The study encompassed individuals between the ages of 18 and 80 years, who were diagnosed with acute ischemic stroke resulting from small vessel occlusion and also received approval from the Hospital's Ethics Committee. The patients and their families signed informed consent forms for acceptance of the intervention procedure and the use of arterial injection of tirofiban.

Exclusion criteria

The following patients were excluded from the study: Patients who had received treatment prior to admission; patient who presented contraindications to digital subtraction angiography; patients who refused to participate; patients who had large vessel occlusive stroke; patients who exhibited psychiatric disorders; or patients who were pregnant. This stringent exclusion criteria ensured a more focused and specific cohort for analysis.

Treatment protocol and grouping

Non-Tirofiban group received oral antiplatelet drugs, i.e. aspirin enteric-coated tablets (100 mg/tablet, Bayer) and clopidogrel hydrogen sulfate tablets (75 mg/tablet, Sanofi), once a day. Tirofiban group was administered 8 - 10 mL of tirofiban hydrochloride sodium chloride injection (100 ml/bottle, Yanda) as per the study protocol via an arterial catheter, followed by continuous intravenous infusion of 6 - 8 ml/hour of tirofiban for 24 - 72 h. A follow-up cranial CT scan was conducted 24 hours post-treatment and in the absence of any bleeding complications, oral antiplatelet aggregation drugs (including tirofiban hydrochloride sodium chloride injection) and dual antiplatelet therapy (consisting of enteric-coated aspirin tablets 100 mg + clopidogrel hydrogen sulfate tablets 75 mg) were administered concurrently for a duration of 4 - 6 hours.

Evaluation of parameters/indices

A head CT scan was performed 24 hours after administration of Tirofiban to determine the presence of intracranial hemorrhage and if the patient experienced any deterioration in neurological function, an immediate repeat CT scan was performed.

Neurological function was evaluated using the National Institutes of Health Stroke Scale (NIHSS) at admission and at 24 h, 72 h, and 7 days after Tirofiban injection. The modified Rankin Scale (mRS) and Barthel Index were used to assess the patient's prognosis 90 days after treatment. A 0 - 2 point mRS score at 90 days was considered a good prognosis, while a score of 3 - 6 points was considered a poor prognosis.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) 26.0 (IBM, Armonk, NY, USA). Normally distributed continuous data was expressed as mean ± standard deviation (SD) and independent sample t-tests were used for inter-group comparisons, while paired-sample t-tests were used for within-group comparisons, before and after treatment. Non-normally distributed data were expressed as median (interquartile range) and Mann-Whitney U test was used for inter-group comparisons, while the Wilcoxon test was used for within-group comparisons, before and after treatment. Categorical data were expressed as numbers and percentages while the chi-square test was used for inter-group comparisons. Application of the Generalized Estimating Equation (GEE) was employed to analyze the variation in NIHSS scores across different time points. Statistical significance was determined by a *p*-value of less than 0.05, indicating the presence of significant findings.

RESULTS

Patient characteristics

A total of ninety (90) patients were enrolled in this study. non-Tirofiban group consisted of forty individuals, with a male-to-female ratio of 31:9 and a mean age of (63.88 ± 9.30) years. Tirofiban group included fifty (50) patients, with a male-to-female ratio of 39:11 and a mean age of (62.44 ± 8.58) years. There were no significant differences in age, sex, past medical history (including stroke, intracerebral hemorrhage, hypertension, diabetes, atrial fibrillation and hyperlipidemia), personal history of indulgence (including smoking and alcohol consumption), blood parameters (lipid profile, INR and homocysteine) and pre-treatment neurological function scores (mRS and BI scores) between the two groups ($p > 0.05$).

Improvement of neurological function

Generalized estimating equations were employed for the analysis. The median NIHSS scores at admission were 4 points for both groups, with no statistically significant difference between the two groups ($p > 0.05$). Following 24 hours of treatment, the median NIHSS score was 4 points in non-Tirofiban group and 3 points in Tirofiban group ($p > 0.05$). At the 72-hour mark, the median NIHSS score was 3 points in both groups. After 7 days of treatment, the median NIHSS score decreased to 2.5 points in non-Tirofiban group and 2 points in Tirofiban group, demonstrating a statistically significant difference between the two groups ($p < 0.05$). Results are presented in Table 1.

Table 1: Comparison of NIHSS score before and after treatment between the two groups

Time-point	Non-Tirofiban group (n = 40)	Tirofiban group (n = 50)	*Wald* χ^2	*P*-value
Admission	4.00 (3.00, 5.00)	4.00 (2.00, 5.25)	0.903	0.342
24 hours treatment	4.00 (3.00, 4.00)	3.00 (2.00, 5.00) [a]	1.978	0.160
72 hours of treatment	3.00 (2.00, 4.00) [a b]	3.00 (2.00, 0.00) [a b]	5.371	0.020
7 days of treatment	2.50 (2.00, 4.00) [a b c]	2.00 (1.00, 3.00) [a b c]	9.532	0.002
Wald χ^2	43.663	101.858	-	-
P-value	< 0.001	< 0.001	-	-

[a]Compared with Admission, [b] compared with 24 hours treatment, [c] compared with 72 hours treatment. $P < 0.05$ is statistically significant

Changes in NIHSS scores of patients after treatment for neurological deficits

There were statistically significant differences in NIHSS scores between Tirofiban group and non-Tirofiban group after 24 hours ($p = 0.046$), 72 hours ($p < 0.001$) and 7 days ($p < 0.0001$) of treatment when compared to pre-treatment scores. There was no statistically significant difference in NIHSS scores between non-Tirofiban group and the pre-treatment group after 24 hours of treatment ($p > 0.05$). However, statistically significant differences were observed after 72 hours ($p = 0.01$) and 7 days ($p < 0.0001$) of treatment, indicating notable variations in NIHSS scores (Figure 1).

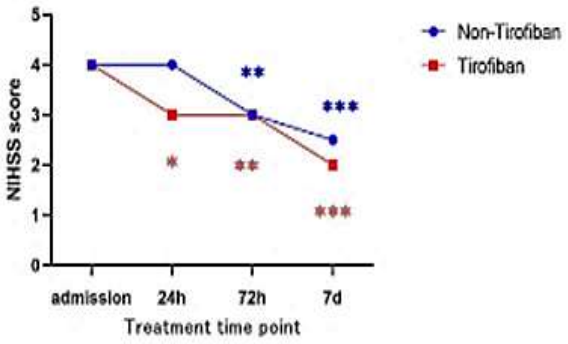

Figure 1: Median changes in NIHSS score before and after treatment in both groups. *$P = 0.046$), **$p < 0.001$ and ***$p < 0.0001$

Early treatment efficacy

Compared with NIHSS scores at admission, the effective rate of treatment after 7 days was 88.0 % (44 / 50) in Tirofiban group and 70.0 % (28 / 40) in non-Tirofiban group, with a statistically significant difference between the two groups (χ^2 = 4.656, p = 0.031) (Table 2).

Table 2: Comparison of effective rate between 7 days and 90 days

Group	7-day effective rate (%)	90-day response rate (%)	X^2	*P*-value
Non-Tirofiban	70.0	72.5	4.656	0.031
Tirofiban	88.0	96	9.931	0.02

90-day prognostic scores for patients

For non-Tirofiban group, the median mRS score at 90 days was 1 (0.00, 3.00), which was statistically different from Tirofiban group's median score of 0 (0.00, 1.00) (Z = -2.224, p = 0.026). The results are presented in Figure 2. The median BI score at 90 days for non-Tirofiban group was 100 (91.25, 100.00), which was statistically different from Tirofiban group's median score of 100 (100.00, 100.00) (Z = -3.171, p = 0.002) (Figure 3).

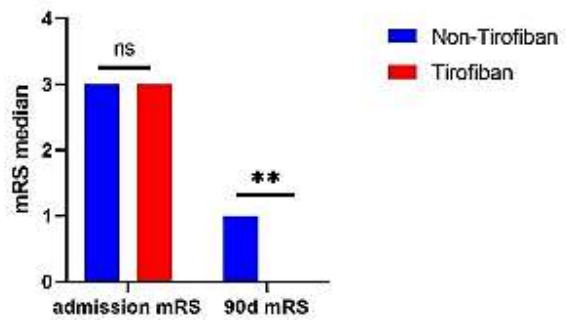

Figure 2: mRS score before treatment and at 90 days of treatment. ns = non-significant; **p < 0.05

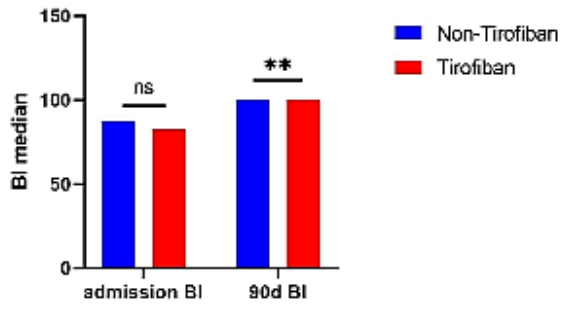

Figure 3: BI scores before treatment and 90 days of treatment. ns = non-significant; *p < 0.05

Patient 90-day prognostic score

Non-Tirofiban group had a good prognosis of 72.5 %, while Tirofiban group was 96.0 %, with a statistical difference between the two groups (χ^2 = 9.931, p = 0.002) (Figure 4).

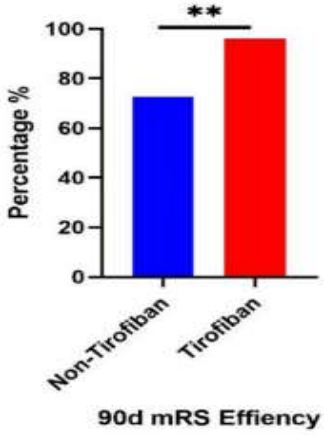

Figure 4: The response rate of mRS (modified Rankin Scale) at 90 days following treatment. **P < 0.05

Adverse reactions in patients after treatment

No case of cerebral hemorrhage occurred in the included patients. non-Tirofiban group had one (01) case of gastrointestinal bleeding and two (02) deaths, but further comparison showed no significant difference in adverse reactions (cerebral hemorrhage, gastrointestinal bleeding, hematuria, skin and mucous membrane bleeding, oral and gingival bleeding, death) between the two groups (p > 0.05).

DISCUSSION

For patients with acute ischemic stroke within the time window for thrombolysis, only antiplatelet aggregation treatment can be chosen [8]. Studies have shown that the combination of clopidogrel and aspirin is more effective than monotherapy, although the risk of hemorrhagic stroke is relatively higher in combination therapy, lasting more than one year [9]. At the same time, the combination of clopidogrel and aspirin does not increase the risk of bleeding and some subtypes of acute cerebral infarction patients obtained the most significant clinical benefits from dual antiplatelet therapy, especially in cases of multiple acute infarctions [10]. For non-disabling cerebrovascular events, dual antiplatelet therapy reduced the risk of stroke recurrence and is now widely used for such patients [11]. The patients included in this study were acute ischemic stroke patients with small vessel disease. In order to better improve the prognosis of the patients, dual

antiplatelet aggregation treatment was selected in the acute phase.

Clopidogrel is an inactive prodrug that needs to be converted into an active metabolite through cytochrome P450 (CYP450) enzymes. Genetic variations, such as allelic genes CYP2C19*2 and *3, have been associated with functional protein loss, resulting in decreased levels of active clopidogrel metabolites and increased platelet reactivity. These factors may consequently elevate the risk of subsequent ischemic events [12,13]. In comparison to other ethnicities, Asians exhibit a higher frequency (ranging from 13 % to 23 %) of poor metabolizer genotypes of CYP2C19, whereas the frequency in other ethnicities ranges from 2 to 5 % [14]. Age, gender, weight, drugs and genes affects the pharmacokinetics of clopidogrel, thereby affecting its antiplatelet effect [15]. Similarly, both aspirin and clopidogrel, as antiplatelet drugs, exhibits drug resistance and affects the outcome and prognosis of patients by affecting their antiplatelet aggregation effects [16]. Furthermore, in the early stages of acute ischemic stroke, it is crucial for patients to rapidly and effectively achieve antiplatelet effects, as oral antiplatelet drugs require absorption through the intestines to exert their effect. In comparison to oral antiplatelet aggregation drugs, tirofiban serves as a glycoprotein (GP) IIb-IIIa inhibitor that specifically targets the final common pathway of platelet aggregation. By inhibiting the binding of adjacent platelets to fibrinogen molecules, tirofiban exhibits a short-acting, reversible and selective antiplatelet aggregation effect [17].

Clinical studies have shown that there is an early risk of re-occlusion in patients with large-vessel occlusion stroke associated with intracranial atherosclerotic stenosis [18]. Intravenous injection of tirofiban reduces the rate of early re-occlusion without increasing the risk of substantial hemorrhage, symptomatic bleeding, 90-day favorable outcomes, or death rate [19]. Further analysis found that the only independent predictor of early re-occlusion was the non-use of intravenous injection of tirofiban, indicating that tirofiban has a beneficial effect on large-vessel occlusive stroke. Tirofiban monotherapy does not significantly increase the risk of cerebral hemorrhage, symptomatic cerebral hemorrhage, or death rate in AIS patients. When used in combination with intravenous thrombolysis, tirofiban does not increase adverse reactions either [20]. In AIS patients who received intravenous thrombolysis or bridging therapy, there was no increased risk of sICH, ICH, or death rate and the early injection of tirofiban improved the 90 - day favorable (mRS ≤ 2) prognosis, indicating that it may be effective and safe [21]. The adverse reaction of cerebral hemorrhage in acute ischemic stroke patients may be related to an NIHSS scores greater than 15 points [17]. However, all patients included in this study had an NIHSS score less than 15 points. In summary, intravenous injection of tirofiban is a safe treatment for acute ischemic stroke.

Studies have shown that there is no difference in the rates of vascular recanalization, NIHSS score at 24 hours, 90-day mRS, or symptomatic intracranial hemorrhage between patients who received arterial injection of tirofiban during mechanical thrombectomy and those who do not receive tirofiban, suggesting that arterial injection of tirofiban is safe [22]. Tirofiban treatment for AIS does not increase the risk of symptomatic bleeding or death rate, but it may increase the risk of fatal cerebral hemorrhage. Arterial administration of tirofiban is associated with an increased risk of fatal cerebral hemorrhage, while intravenous administration is not. In addition, tirofiban does not significantly improve functional outcomes (mRS ≤ 2) [23]. Following intravenous tissue-type plasminogen activator (tPA) thrombolysis, the administration of arterial tirofiban injection has shown no significant differences in symptomatic cerebral hemorrhage, 3-month mortality rate, or 3-month favorable prognosis (mRS ≤ 2). These findings suggest that tirofiban does not significantly influence the outcomes of patients with acute ischemic stroke [24]. However, current studies continue to present conflicting evidence regarding the safety and efficacy of arterial tirofiban injection, thereby generating ongoing debate within the scientific community.

This study selected arterial injection of tirofiban to investigate the effect of antiplatelet aggregation drugs on the time window of acute ischemic stroke. From a safety perspective, the incidence of adverse reactions in patients using arterial tirofiban did not increase, but there was one case of gastrointestinal bleeding and two deaths in the group of patients taking oral antiplatelet drugs, although the difference was not statistically significant. Gastrointestinal bleeding is a complication of dual antiplatelet therapy, which is related to the mechanism of drug action. Proper use of proton pump inhibitors prevents gastrointestinal bleeding to some extent [25]. In contrast, there is currently no literature

documenting any specific detrimental effects of tirofiban on the gastrointestinal mucosa. From an effective responsiveness perspective, with the application of antiplatelet aggregation, neurological function deficit symptoms in stroke patients have consistently demonstrated varying degrees of recovery. However, patients who received arterial injection of tirofiban had a significant improvement in NIHSS at 72 hours and 7 days compared to those who did not use tirofiban. Long-term follow-up found that arterial injection of tirofiban also had a good prognosis for the mRS score at 90 days.

Limitations of this study

This study suggests that arterial injection of tirofiban is safe and effective but the treatment scope was narrow. For future studies on arterial injection of tirofiban for the treatment of acute ischemic stroke, it is imperative to broaden the treatment scope and gather more robust and reliable data in order to enhance the quality of evidence in this field.

CONCLUSION

Arterial administration of tirofiban has the potential to enhance recovery of neurological function in hyper-acute stroke cases that exceed typical time window for treatment. Moreover, it demonstrates efficacy in improving late-life treatment outcomes while maintaining a favorable safety profile without an increased incidence of adverse reactions. Therefore, tirofiban is a promising and safe antiplatelet aggregation drug for hyper-acute ischemic stroke cases that fall outside the conventional treatment window.

DECLARATIONS

Acknowledgements

This study was supported by the Scientific Research Project of Health Industry in Hainan Province (no. 22A200248), Hainan Province Research and Development Project (no. ZDYF2021SHFZ092) and also the Project Supported by Hainan Province Clinical Medical Center.

Funding

None provided.

Ethical approval

This study was approved by the Ethics Committee of The First Affiliated Hospital of Hainan Medical University (approval no. 20 – HMU – 201).

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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