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Original Article

Safety and efficacy of intravenous Tirofiban infusion after mechanical thrombectomy in acute ischemic stroke: a retrospective observational study

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Abstract: Objective: To investigate the safety and efficacy of intravenous Tirofiban infusion after mechanical thrombectomy in patients with acute ischemic stroke. Methods: A consecutive series of patients with acute ischemic stroke who underwent mechanical thrombectomy were included. The patients were categorized into two groups according to whether they received intravenous Tirofiban infusion after mechanical thrombectomy. Intracranial hemorrhage (ICH) and all-cause mortality were studied as safety outcomes; recanalization of target vessel evaluated by thrombolysis in cerebral infarct (TICI) scale, and neurological improvement evaluated by Institutes of Health Stroke Scale (NIHSS) and modified Rankin scale (mRS) were studied as efficacy outcomes. Results: A total of 31 patients who underwent mechanical thrombectomy were enrolled, among which 8 (25.81%) received a standard dose of intravenous Tirofiban infusion after mechanical thrombectomy. There was no significant difference in baseline characteristics between the two groups (all P>0.05). None (0.00%) of the patients suffered ICH in the Tirofiban group, while 3 (13.04%) suffered ICH in the control group (P=0.550); similar all-cause mortality rates were found in both groups (25.00% versus 17.39%, P=0.634). In the Tirofiban group, all patients achieved successful recanalization defined by TICI groups (25.00% versus 17.39%, P=0.634). In the und in both groups (25.00% versus 17.39%, P=0.634). In th4). In thle, and neurological improvement evaluated so, 'et al' is notned by 3-month mRS≤2, which were not statistically significant when compared to the control group (all P>0.05). Conclusion: Intravenous Tirofiban infusion after mechanical thrombectomy is safe and effective in patients with acute ischemic stroke.

Keywords: Tirofiban, glycoprotein IIb/IIIa inhibitors, acute ischemic stroke, thrombectomy, outcomes research

Introduction

Stroke is a leading cause of mortality and disability, which has caused substantial economic costs of treatment and post-stroke care worldwide [1, 2]. Although the past decade saw a decrease in death rate and prevalence of stroke with substantial advances in the diagnostic and treatment options, there is still a high overall burden of stroke [3]. Timely restoration of blood flow using thrombolytic therapy is the most effective maneuver for salvaging ischemic brain tissue that is not infarcted yet, and mechanical thrombectomy is one of the options for reperfusion therapy which is proven to be effective [4-6]. However, re-occlusion may still occur after initial recanalization via mechanical thrombectomy which leads to worse outcome [7].

To further improve prognosis of patients with acute ischemic stroke receiving mechanical thrombectomy, investigational methods are being explored, including combined intravenous glycoprotein (GP) IIb-IIIa inhibitors Tirofiban [8-10]. GP IIb-IIIa inhibitors are antiplatelet agents which prevent platelet aggregation by antagonizing GP IIb-IIIa receptors on the surface of platelet [11]. Compared with conventional antiplatelet agents such as aspirin or

clopidogrel, GP IIb-IIIa inhibitor has a more profound antiplatelet effect with more rapid onset, since it provides an endogenous thrombolysis effect by inhibiting fibrinogen, and thus reducing thrombus growth or re-formation [8]. GP IIb-IIIa inhibitors are currently suggested to be used in patients with acute coronary syndromes and during coronary angioplasty, but its role in ischemic stroke remains unknown. The conclusion from a meta-analysis which included four trials involving 1365 participants did not support the routine use of GP IIb-IIIa inhibitors (mainly Abciximab) in patients with ischemic stroke given that its use was associated with a significant risk of intracranial hemorrhage without any reduction in death or disability [8]. The SaTIS Trial, however, suggests that Tirofiban may be safe in moderate-acute ischemic stroke even when administered within a broad time window after symptom onset and may save lives in the late outcome [10]. Safety and preliminary efficacy were also observed in an observational study that included patients with acute ischemic stroke who received alteplase followed by intravenous Tirofiban infusion [9]. These controversial results warrant further investigations. Our present study aimed to investigate the safety and efficacy of intravenous Tirofiban infusion after mechanical thrombectomy in patients with acute ischemic stroke.

Materials and methods

Patients

The study retrospectively included a consecutive series of patients (n=31) with acute ischemic stroke who underwent mechanical thrombectomy between May 2019 and August 2020 in the Department of Neurology of Jinan People's Hospital Affiliated to Shandong First Medical University by screening data from the hospital information system. The study was approved by the Institutional Review Board of Jinan People's Hospital Affiliated to Shandong First Medical University and informed consent was waived since the study was a retrospective observational study and only anonymous data were used.

Diagnosis and initial management of acute ischemic stroke

The diagnosis and standard management of acute ischemic stroke during the study period followed the Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2018 and Chinese Guidelines for the Endovascular Treatment of Acute Ischemic Stroke 2018 [12, 13]. In brief, for patients who are suspected of ischemic stroke, vital signs should be immediately assessed to ensure stabilization of airway, breathing, and circulation, and patient history should be obtained rapidly followed by a physical examination. Neuroimaging either computed tomography (CT) or magnetic resonance imaging (MRI) should be performed as soon as possible to confirm the diagnosis of ischemic stroke. Initial treatment including the management of volume depletion, electrolyte disturbances, fever, hypoglycemia or hyperglycemia, concomitant acute cardiac ischemia, and blood pressure should be performed once the diagnosis was established.

Intravenous thrombolysis

For onset of ischemic stroke within 4.5 h, patients were strictly screened according to the indications and contraindications of intravenous thrombolysis, and received intravenous recombinant tissue plasminogen activator (rtPA, Actilyse, Alteplase for injection, Boehringer Ingelheim) thrombolytic therapy as soon as possible. The dosing of rtPA was 0.9 mg/kg (maximum dose is 90 mg), of which the first 10% was intravenously injected in the first 1 minute (min), and the rest was infused continuously for 1 h. For onset of ischemic stroke within 6 h, intravenous thrombolysis with urokinase was considered, where 1-1.5 million IU urokinase was dissolved in 100-200 mL of normal saline followed by continuous intravenous drip for 30 min. Decision on intravenous thrombolysis was not affected by whether mechanical thrombectomy was indicated.

Mechanical thrombectomy

Criteria for mechanical thrombectomy included: (1) a modified Rankin scale (mRS) score before onset of 0 or 1; (2) intracranial arterial occlusion of the distal intracranial internal carotid artery (ICA), or the M1 segment of the middle cerebral artery (MCA) demonstrated with CT angiography, MR angiography, or digital subtraction angiography; (3) age ≥18 years; (4) the National Institutes of Health Stroke Scale (NIHSS) ≥6 points; (5) femoral puncture could start within 6 h of symptom onset; (6) ischemic

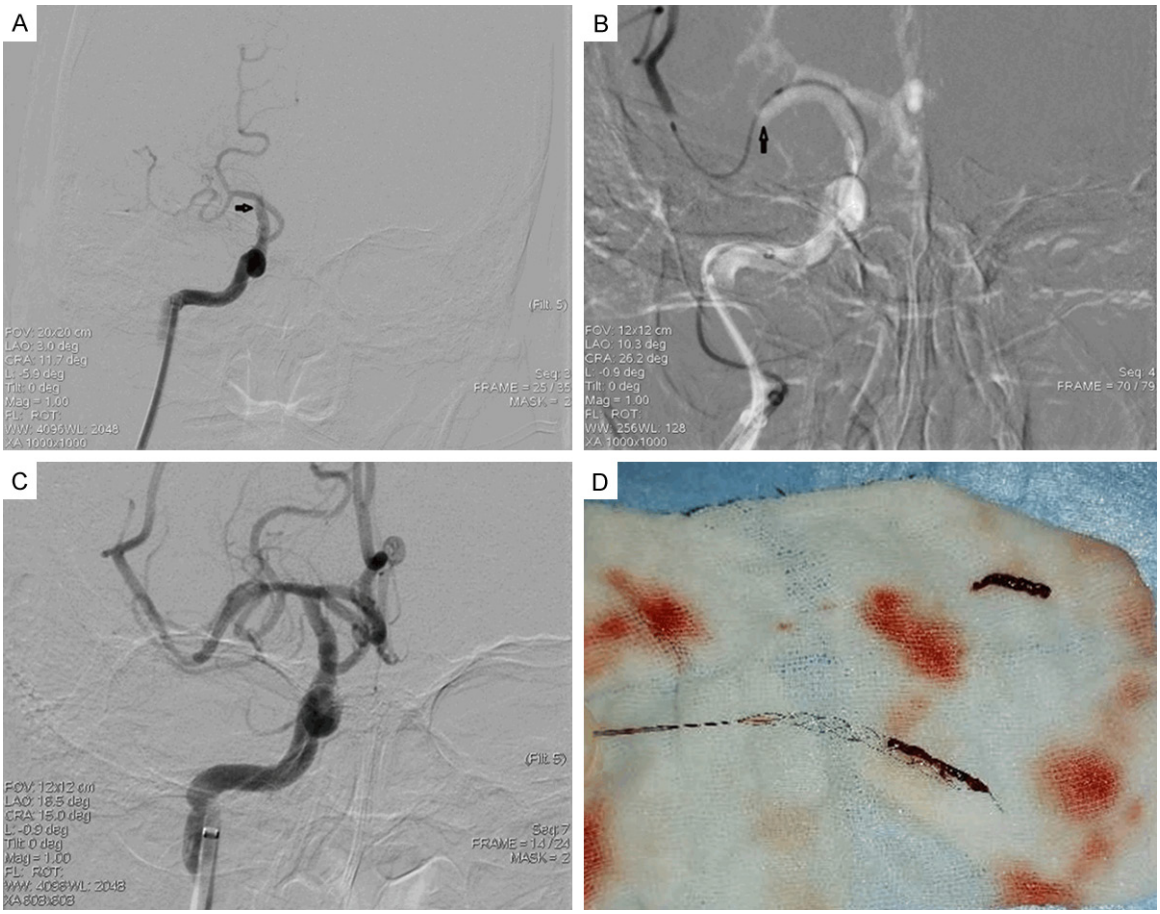

Figure 1. Procedures of mechanical thrombectomy. A: L-MCA M1 occlusion revealed by DSA; B: The microcatheter was guided to the distal end of the target vessel with the assistance of a guide catheter within blood vessel; C: DSA showed successful recanalization of the occlusion presented in **Figure 1A**; D: The removed fresh thrombus.

stroke caused by a large artery occlusion in the proximal anterior circulation within 24 h after onset and meeting the eligibility criteria of the DAWN trial [14].

Mechanical thrombectomy was performed in the following way: (1) the patient was in the supine position, and after general anesthesia, the right femoral artery was punctured using Seldinger technique, and an 8-F sheath (Cordis, USA) was inserted; (2) after systemic heparinization, an 8-F Merci Balloon Guide Catheter (Concentric Medicalgon, USA), of which the head end was delivered to the proximal end of the target vessel, and the angiography was used to examine the location, degree, and collateral compensation of the occlusion of the artery; (3) Trevo Pro18 microcatheter (Stryker, USA) was guided to the distal end of the target vessel with the coaxial assistance of Traxcess microwire (MicroVention, USA) and DAC 057/044 distal support catheter (Stryker, USA) or 5-F Navien intermediate catheter (eV3, USA); (4) a Trevo Provue stent (Stryker, USA) was deployed to cover the thrombus; (5) the stent and the delivery microcatheter were gently withdrawn with negative pressure aspiration. An example of the main procedures of mechanical thrombectomy is illustrated in **Figure 1**.

Intravenous Tirofiban infusion

During the study period, there was no strict criterion about whether a patient would receive intravenous Tirofiban infusion, and the decisions were made mainly based on the practitioner. In general, the following indications were applied: (1) presence of intracranial large vessel occlusion; (2) vessel recanalization (TICI cranial large vessel occlusion; the decisions were mainly based on practitioner immediately after mechanical thrombectomy) [15]. Tirofiban (5 mg: 100 mL, Grand Pharmaceutical Co.,

Ltd., China) was administered with a bolus of 0.25-0.5 mg at a rate of 1 mL/min followed by a continuous infusion of 0.1 μg/kg/min for 24 h. Once Tirofiban drip was stopped, the regimen was transitioned to aspirin (Aspirin enteric-coated tablets, Bayer; 100 mg/day) and clopidogrel (Clopidogrel hydrogen sulphate tablets, Accord Healthcare; 75 mg/day) daily for the patients.

Outcome measures

ICH and all-cause mortality were studied as safety outcomes, which was evaluated during the hospitalization. A head computerized tomography (CT) scan was performed routinely immediately after mechanical thrombectomy, and extra scan was performed when there was any sign of neurological deterioration. Recanalization of target vessel evaluated by thrombolysis in cerebral infarct (TICI) scale, and neurological improvement evaluated by Institutes of Health Stroke Scale (NIHSS) and modified Rankin scale (mRS) were studied as efficacy outcomes. A TICIICIcal deterioration. Recanalization of target v [16]. NIHSS was evaluated at admission, 24 h and 7 d after admission. A decrease in NIHSS≥4 at 7 d after admission was considered as short-term neurological improvement. mRS before onset was routinely evaluated at admission and 3-month of follow-up. A 3-month mRS≤2 was considered as long-term neurological improvement. The cut-offs for the above scores were widely used in other studies [15, 17].

Statistical analysis

Continuous variables were expressed as mean ± standard deviations ($\bar{x}$±sd) or median (25-75% quartiles); categorical variables were expressed as number (percentage). For continuous variables, comparisons between two groups were examined by 2-sided t test or Kruskal-Wallis H test; for categorical variables, comparisons between two groups were examined by chi-squared test or Fisher exact test. To investigate the association between intravenous thrombolysis and successful recanalization, multivariable logistic regression models were employed, including a model adjusted for age and sex, and a model adjusted for age, sex, and intravenous Tirofiban infusion. The significance level was set at P<0.05. Statistical analysis was performed using SPSS version 22 and R program.

Results

Baseline characteristics of the study population

A total of 31 patients who underwent mechanical thrombectomy were enrolled, with an average age of 61.7±10.7 years. 61.29% of them were male, and 58.06% had hypertension. 80.65% had a large artery atherosclerosis (LAA), and 19.35% had cardioembolism (CE). The most frequent occlusion site was M1 (48.39%), and 16.13% of the patients were wake-up stroke. The average onset NIHSS was 13.71±3.47 and 38.71% received intravenous thrombolysis with a median door-to-needle time of 48.50 (33.50-77.25) min. Among the study population, 8 (25.81%) received a standard dose of Tirofiban intravenously within 24 h after mechanical thrombectomy. Compared with patients who did not receive Tirofiban, patients who received Tirofiban were slightly older (63.38±9.01 versus 61.17±11.37 years, P=0.625), and had a higher proportion of LAA (87.50% versus 78.26%, P=1.000), but the differences were not significant. There was also no significant difference in other baseline characteristics between the two groups (all P>0.05), as shown in **Table 1**.

Safety and efficacy of intravenous Tirofiban infusion

None (0.00%) of the patients suffered ICH in the Tirofiban group, while 3 (13.04%) suffered ICH in the control group (P=0.550); similar all-cause mortality rates were found in the two groups (25.00% versus 17.39%, P=0.634). In the Tirofiban group all patients achieved successful recanalization defined by TICI≥2b compared to 80.95% in the control group; 3 (75.00%) had favorable short-term neurological improvement defined by a decrease in NIHSS≥4 at 7 d compared to 70.59% in the control group (**Figure 2**); 3 (75.00%) had favorable long-term neurological improvement defined by 3-month mRS3 compared to 80.95% in the control group (P>0.05, **Table 2**).

Association between intravenous thrombolysis and successful recanalization

Among the study patients, receiving intravenous thrombolysis (either urokinase or rtPA) was associated with higher probability of successful recanalization (defined as TICI with higher probability of successful recanalization,

Table 1. Baseline characteristics of the study population

Variable	Total (n=31)	Intravenous Tirofiban infusion within 24 hours after mechanical thrombectomy		P
		No (n=23)	Yes (n=8)	
Age (years)	61.7±10.7	61.2±11.4	63.4±9.0	0.625
Sex (n)				1.000
Male	19 (61.29%)	14 (60.87%)	5 (62.50%)	
Female	12 (38.71%)	9 (39.13%)	3 (37.50%)	
Comorbidities (n)				
Hypertension	18 (58.06%)	13 (56.52%)	5 (62.50%)	1.000
Diabetes	3 (9.68%)	2 (8.70%)	1 (12.50%)	1.000
Coronary heart disease	2 (6.45%)	1 (4.35%)	1 (12.50%)	0.456
Atrial fibrillation	6 (19.35%)	5 (21.74%)	1 (12.50%)	1.000
Current smoker	9 (29.03%)	6 (26.09%)	3 (37.50%)	0.660
Subtypes of ischemic stroke (TOAST; n)				1.000
Large artery atherosclerosis (LAA)	25 (80.65%)	18 (78.26%)	7 (87.50%)	
Cardioembolism (CE)	6 (19.35%)	5 (21.74%)	1 (12.50%)	
Occlusion site (n)				
M1	15 (48.39%)	10 (43.48%)	5 (62.50%)	0.433
M2	3 (9.68%)	2 (8.70%)	1 (12.50%)	1.000
C1	2 (6.45%)	2 (8.70%)	0 (0.00%)	1.000
C2	1 (3.23%)	1 (4.35%)	0 (0.00%)	1.000
C6	2 (6.45%)	1 (4.35%)	1 (12.50%)	0.456
C7	11 (35.48%)	9 (39.13%)	2 (25.00%)	0.676
BA	1 (3.23%)	1 (4.35%)	0 (0.00%)	1.000
Wake-up stroke (n)	5 (16.13%)	4 (17.39%)	1 (12.50%)	1.000
NIHSS onset	13.71±3.47	13.65±3.82	13.88±2.36	0.879
MRS before onset	0 (0-0)	0 (0-0)	0 (0-0)	0.555
Intravenous thrombolysis				0.835
No	19 (61.29%)	15 (65.22%)	4 (50.00%)	
Urokinase	8 (25.81%)	5 (21.74%)	3 (37.50%)	
Recombinant tissue plasminogen activator (rtPA)	4 (12.90%)	3 (13.04%)	1 (12.50%)	
Door to needle time (min)	48.5 (33.5-77.3)	52.0 (44.8-77.3)	40.0 (29.8-71.0)	0.593
Onset to puncture time (min)	292.5 (245.3-354.0)	285.0 (245.3-342.0)	312.0 (255.0-357.5)	0.673
Door to puncture time (min)	125.0 (97.5-153.0)	130.0 (102.5-155.0)	105.0 (95.3-120.8)	0.223

Note: NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin scale.

P=0.4832). Results were consistent after adjusted for potential confounding factors including intravenous Tirofiban infusion (OR 2.87, 95% CI 0.21-39.86, P=0.4318, **Table 3**).

Discussion

In this study, we retrospectively analyzed patients with acute ischemic stroke who received mechanical thrombectomy and compared the safety and efficacy outcomes of patients who received intravenous Tirofiban infusion within 24 h after mechanical thrombectomy with the patients who did not. Theoretically, Tirofiban may help improve the effectiveness of recanalization but it also raises concerns about risk of bleeding. Our results suggested that intravenous Tirofiban infusion within 24 h after mechanical thrombectomy appeared to be safe and effective in patients with acute ischemic stroke. Considering the increasing use of mechanical thrombectomy in patients with ischemic stroke, evidence about adjunctive therapies such as use of Tirofiban might be helpful to further improve prognosis of patients receiving mechanical thrombectomy [18, 19]. In addition, we investigated the association between intravenous thrombolysis and successful recanalization and found that receiving intravenous

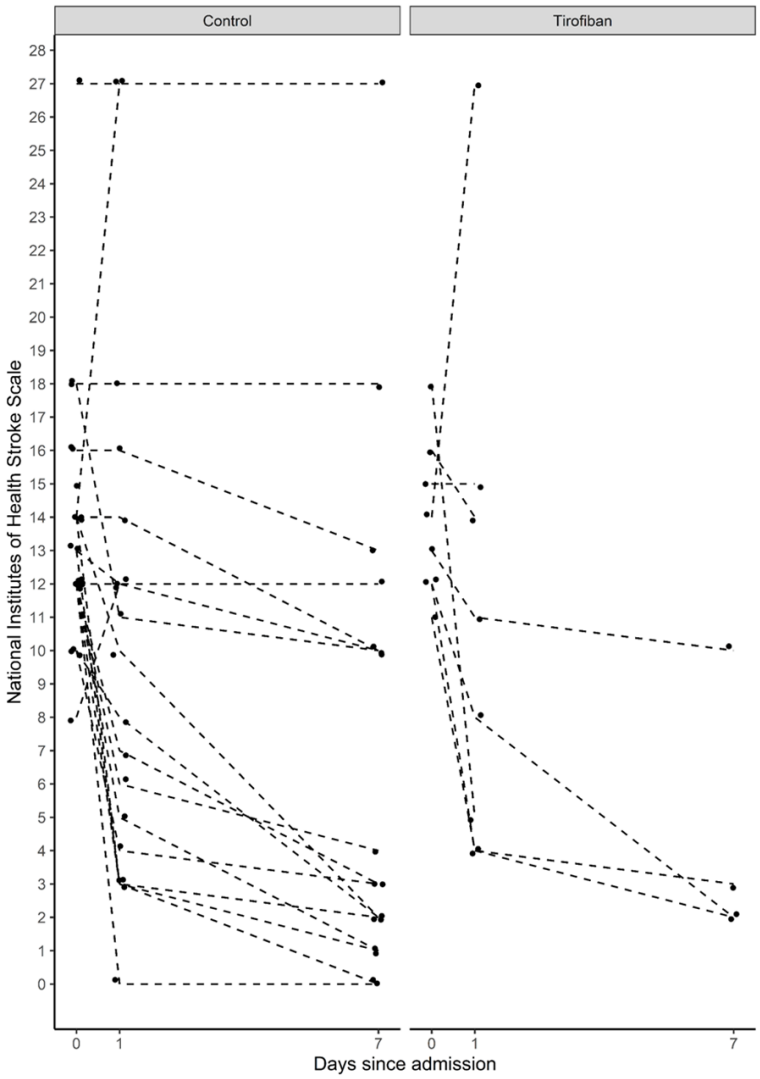

Figure 2. Change of National Institutes of Health Stroke Scale (NIHSS) of the study population. The figure presents the changes of National Institutes of Health Stroke Scale (NIHSS) of the studied patients at admission (day 0), day 1 and day 7 after admission. The left panel presents patients who did not receive intravenous Tirofiban infusion after mechanical thrombectomy, and the right panel presents patients who received intravenous Tirofiban infusion after mechanical thrombectomy.

thrombolysis was associated with higher probability of successful recanalization. This finding, to some extent, supports the current guideline that mechanical thrombectomy should not prevent the initiation of intravenous thrombolysis where this is indicated.

Although early arterial recanalization is associated with better prognosis of patients with acute ischemic stroke, re-occlusion could still occur after initial recanalization via mechanical thrombectomy, leading to worse outcome [7]. Antiplatelet agents including aspirin and clopidogrel are routinely used for reducing recurrent stroke, but it remains unknown whether it is effective to prevent early re-occlusion after successful mechanical thrombectomy. A study that included 711 acute ischemic stroke patients reported that 2.3% patients had early re-occlusion within 48 h (median 20 h) after successful mechanical thrombectomy, which was associated with an unfavorable outcome at 90 d [20]. Considering the relatively short interval between reperfusion and re-occlusion, GP IIb-IIIa inhibitor Tirofiban administered via intravenous infusion might provide a more profound antiplatelet effect with more rapid onset when compared to the conventional antiplatelet agents. Tirofiban shows a dose-dependent inhibition of *ex vivo* platelet aggregation within minutes of bolus administration, and the inhibitory effect is maintained during continuous drug infusion [21]. In clinical practice for the treatment of patients with coronary disease, the effectiveness of Tirofiban has been observed [22, 23]. For patients with unstable angina or non-ST elevation myocardial infarction undergoing percutaneous coronary intervention (PCI), several trials confirmed that use of Tirofiban reduced recurrent ischemia requiring repeat PCI [22, 23]. However, evidence about the use of Tirofiban in patients with acute ischemic stroke is relatively limited, especially for patients who received mechanical thrombectomy.

A concern about the use of Tirofiban is the increased risk of ICH, which was supported by a meta-analysis. However, the studies included in the meta-analysis were mainly using

Table 2. Prognosis of the study population

Variable	Total (n=31)	Intravenous Tirofiban infusion within 24 hours after mechanical thrombectomy		P
		No (n=23)	Yes (n=8)	
Intracerebral hemorrhage (ICH; n)	3 (9.68%)	3 (13.04%)	0 (0.00%)	0.550
Mortality after mechanical thrombectomy (n)	6 (19.35%)	4 (17.39%)	2 (25.00%)	0.634
TICI (n)				0.637
0	1 (3.45%)	1 (4.76%)	0 (0.00%)	
1	1 (3.45%)	1 (4.76%)	0 (0.00%)	
2a	2 (6.90%)	2 (9.52%)	0 (0.00%)	
2b	4 (13.79%)	2 (9.52%)	2 (25.00%)	
3	21 (72.41%)	15 (71.43%)	6 (75.00%)	
Successful recanalization (TICI≥2b; n)	25 (86.21%)	17 (80.95%)	8 (100.00%)	0.552
Onset to Recanalization Time (minutes)	315 (284-412)	314 (260-380)	373 (298-413)	0.336
Door to Recanalization Time (minutes)	200.50 (188.75-219.75)	203.00 (194.75-225.25)	192.00 (177.25-206.00)	0.244
NIHSS at 24 h	10.0 (4.5-14.0)	10.0 (4.5-13.0)	9.5 (4.8-14.3)	0.790
NIHSS at 7 d	3 (2-10)	3 (2-10)	3 (2-5)	0.751
Short term neurological improvement (decrease in NIHSS at 7 d ≥4)	15 (71.43%)	12 (70.59%)	3 (75.00%)	1.000
MRS at 3 m	1 (0-3)	1 (0-3)	0 (0-1)	0.181
Long term neurological improvement (mRS at 3 m ≤2)	13 (59.09%)	10 (55.56%)	3 (75.00%)	0.616

Note: ICH: Intracerebral hemorrhage; TICI: Thrombolysis in Cerebral Infarction; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin scale.

Table 3. Association between intravenous thrombolysis and successful recanalization

	Odds ratio	95% confidence interval	P
Crude model			
No	1 (Reference)	-	-
Yes	2.36	0.21-25.91	0.4832
Model 1			
No	1 (Reference)	-	-
Yes	3.34	0.27-41.84	0.3504
Model 2			
No	1 (Reference)	-	-
Yes	2.87	0.21-39.86	0.4318

Note: Model 1 was adjusted for age and sex; model 2 was adjusted for age, sex, and intravenous Tirofiban infusion.

Abciximab instead of Tirofiban [8]. Several studies confirmed the safety of using Tirofiban in patients received mechanical thrombectomy, but results about the efficacy remained controversial. Kang et al. investigated the safety and effectiveness of low-dose intra-arterial Tirofiban in instant re-occlusion after mechanical thrombectomy of *in situ* thromboocclusion [24]. Zhang et al. investigated the use of intra-arterial Tirofiban in ischemic stroke patients after unsuccessful mechanical thrombectomy and confirmed the safety of Tirofiban [25]. Similar results were reported by Yu et al., but the study showed no beneficial effect on prognosis when using low dose intra-arterial Tirofiban in mechanical thrombectomy during acute ischemic stroke [26]. Considering the dose-dependent effect of Tirofiban, continuous intravenous Tirofiban administration might benefit patients more when compared to intra-arterial Tirofiban. Cheng et al. investigated the safety and efficacy of intravenous administration of a standard dose of Tirofiban after vessel recanalization by mechanical thrombectomy in acute ischemic stroke, and the results suggested the therapy appeared to be safe and relatively effective; however, the study did not include a group of patients who underwent mechanical thrombectomy without intravenous Tirofiban [15]. In our study, we retrospectively compared the safety and efficacy outcomes among patients with acute ischemic stroke who received intravenous Tirofiban infusion within 24 h after mechanical thrombectomy and those who did not. Results of our study were consistent with the study of Cheng et al. [15]. Compared with the control group, we found that intravenous Tirofiban infusion appeared to have better efficacy outcomes (100% successful recanalization versus 80.95%; 75.00% short term neurological improvement versus 70.59%; and 75.00% long term neurological improvement versus 55.56%). However, all the differences were non-significant, which might be due to the limited sample size. In terms of safety outcome, although there was still no statistically significant difference between the two groups, the Tirofiban group appeared to have lower ICH (0.00% versus 13.04%), while the mortality rate was slightly higher (25.00% versus 17.39%).

Our findings provided further evidence on the use of intravenous Tirofiban infusion within 24 h after mechanical thrombectomy in acute ischemic stroke, but there were also some limitations that should be noted. First, the study used a retrospective study design, and all the data analyzed could only be retrieved from the existing data. Therefore, in the study, some clinical outcomes contained missing values. Second, the sample size was limited, which might lack power to detect the difference between the two groups. Third, since there were no strict indications for intravenous Tirofiban infusion due to the retrospective study design, confounding by indication therefore could not be ruled out.

In conclusion, intravenous Tirofiban infusion within 24 h after mechanical thrombectomy appears to be safe and effective in patients with acute ischemic stroke, but more studies are needed for further confirmation.

Disclosure of conflict of interest

None.

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