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There is no difference in safety and efficacy with Tirofiban or Eptifibatide for patients undergoing treatment of large vessel occlusion and underlying intracranial atherosclerosis

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ABSTRACT

Background: Glycoprotein IIb/IIIa inhibitor use in acute ischemic stroke (AIS) during mechanical thrombectomy (MT) and acute stenting and angioplasty is a topic consistently debated due to concerns over safety and efficacy. Tirofiban is a glycoprotein IIb/IIIa used throughout the world now more commonly used during MT. We report the analysis of all AIS patients treated with Eptifibatide + MT vs. Tirofiban + MT.

Methods: Using a prospectively collected endovascular database at a CSC between 2013 and 2019, workflow, and outcomes were recorded. Patients are given Tirofiban, and patients given Eptifibatide were analyzed to obtain baseline demographics, modified Ranking Scale (mRS) at discharge, and 90 days follow up, pre and post thrombolysis in cerebral infarction (TICI), mortality rate, and hemorrhage rates.

Results: A total of 571 MT patients were treated: of those, 89 patients (average age 69.25 ± 14.21, 25.84% female) with underlying intracranial atherosclerosis were treated with a GpIIb/IIIa inhibitor. Analysis of 40.45% (36/89) patients treated with Tirofiban + MT and 59.55% (53/89) patients with Eptifibatide + MT was performed. There was no statistically significant difference in NIHSS upon admission ($p = .441$). Four patients (11.11%) in the Tirofiban + MT cohort had symptomatic hemorrhage versus four patients (7.55%) in the Eptifibatide + MT cohort ($p = .564$). There was no significant difference in mortality ($p = .573$) or final recanalization ($p = .678$) between the two cohorts.

Conclusion: Tirofiban use in MT does not increase the risk of symptomatic hemorrhages or mortality compared to Eptifibatide use in MT with acute stenting. Large prospective studies are warranted to confirm the safety/efficacy of Tirofiban in acute ischemic stroke patients treated with mechanical thrombectomy and acute stenting.

1. Introduction

Glycoprotein IIB/IIA inhibitor use during mechanical thrombectomy is becoming an established practice of treating acute ischemic stroke patients with mechanical thrombectomy (MT), pushing for assistance from various medications. Glycoprotein IIb-IIIa inhibitors (Eptifibatide, Tirofiban, Abciximab) are used globally during the treatment of acute stroke patients with underlying intracranial atherosclerosis requiring acute angioplasty and or stenting; Recently, Tirofiban is substituting Eptifibatide use due to decreased cost [1]. Moreover, tissue plasminogen activator (tPA) in conjunction with glycoprotein inhibitors enhances clot's dissolution [2]. Likewise, tPA, in addition to Tirofiban, improves the recanalization rate of a cerebral artery, while the increased risk of hemorrhage has not been documented [3,4].

Previous research has shown that Eptifibatide is the norm of treatment for underlying intracranial atherosclerosis; however, the recent switch to Tirofiban to treat underlying intracranial atherosclerosis is raising concerns of safety and effectiveness. Each GpIIb/IIIa inhibitor prevents the aggregation of platelets through varying processes. For instance, Eptifibatide prevents the ability to bind to the activated

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platelet while Tirofiban inhibits the last common step of thrombi formation [3–5]. Another difference is that Eptifibatide has less receptor affinity than Tirofiban, resulting in dissociation from the receptor faster [3–5]. Both inhibitors have been published on in acute stroke, Chahal et al. demonstrated that Eptifibatide utilized with MT improves patient outcome and safety by suppressing inflammation and prevention of rethrombosis [4,6,7]. While Yu T displayed that Tirofiban facilitates reperfusion of distal vessel while improving patient outcome [3,8,9]. We aim to report on a small cohort of acute ischemic stroke patients and compare those treated with Eptifibatide + MT to those treated with Tirofiban + MT to distinguish differences and similarities in patient outcomes when treating underlying intracranial atherosclerosis with GpIIb/IIIa inhibitors.

2. Methods

A retrospective study was conducted including AIS patients with underlying intracranial atherosclerosis between August of 2013 to January 2019 and from August 2017 to January 2019 across two-stroke centers. The two institutions compiled a prospectively maintained database. One of the two-stroke centers used Eptifibatide from May 2013 to July 2017 and subsequently switched to Tirofiban in August 2018. One of the stroke centers used Tirofiban for very few stroke cases and used Cangrelor for other cases. Eptifibatide was not used at one of the stroke centers. The process for data collection was approved/reviewed at each respective institution.

2.1. Interventional and post procedural parameters

Mechanical thrombectomy cases were treated with a stent retriever and distal catheter aspiration using the Solumbra technique. The regimen of Tirofiban and Eptifibatide used consisted of intravenous administration based on the weight of the patient. The Tirofiban bolus was administered at 12mcg/kg over 30 min. For a detailed administration of intravenous Tirofiban, refer to Table 1. Following this regimen, a maintenance drip for 6–12 h at 0.1 mcg/kg/min and a bolus of 300–600 mg Plavix and 325 mg of aspirin were given.

Similarly, to Tirofiban administration, eptifibatide was administered 2mcg/kg/min bolus intravenously over 30 min, followed by 0.5mcg/kg/min infusion for 6–12 h after 300–600 mg Plavix bolus and 325 mg of aspirin. If the patient presents with a change, a noncontrast CT of the head was performed. If an intracranial hemorrhage was discovered, the glycoprotein IIIB/IIIA was discontinued, and neurosurgery consulted.

Table 1
Tirofiban Protocol/Regimen.

INTRAVENOUS (250 mL bag)			
Weight (kg)	Bolus 12 mcg/kg over 30 min		Infusion Rate 0.1 mcg/kg/min (mL/h)
	Volume (mL)	Rate (mL/h)	
30–37	8	16	4
38–45	10	20	5
46–54	12	24	6
55–62	14	28	7
63–70	16	32	8
71–79	18	36	9
80–87	20	40	10
88–95	22	44	11
96–104	24	48	12
105–112	26	52	13
113–120	28	56	14
121–128	30	60	15
129–137	32	64	16
138–145	34	68	17
146–153	36	72	18

2.2. Data collected

We compiled patient demographic data (i.e., gender, race/ethnicity, age) and co-morbid conditions (i.e., hypertension, diabetes mellitus, atrial fibrillation, cigarette smoking, atrial fibrillation, congestive heart failure, and coronary artery disease) from the prospectively maintained database. Modified Rankin Scale (mRS) score at discharge and NIHSS score upon admission were obtained from the prospectively maintained database. A collection of pre-thrombolysis in cerebral infarction (TICI) and post TICI values were collected as well as symptomatic intracerebral hemorrhage (SICH) and mortality rates. SICH is defined as an ICH on a 24-hour CT scan and a decrease in NIHSS score of 4 or more. Additional data regarding the site of occlusion, recanalization occurrence, and mechanical thrombectomy specifics.

2.3. Statistical analysis

We conducted an analysis consisting of AIS patients receiving mechanical thrombectomy treated with either angioplasty alone or angioplasty with a stent or neither in addition to either Eptifibatide or Tirofiban. We performed univariate analyses to identify differences in baseline characteristics, IV tPA use, and outcomes of both cohorts. The *t*-test was used for continuous variables, and the chi-square test was used for categorical variables. Outcomes analyzed included symptomatic hemorrhage rates, mortality rates at discharge, NIHSS score upon admission, mRS 0–2 scores at discharge, and TICI score 2b-3. Logistic regression analyses were performed to determine the correlation between MT + Tirofiban/MT + Eptifibatide and (1) symptomatic hemorrhage, (2) mortality rate at discharge, (3) good outcome at discharge (0–2), (4) good TICI score (2b-3). All variables that were determined to be significant in the univariate analysis were added to the logistic regression model. In the model analysis, the variables that were included are atrial fibrillation (AF) rate (categorical), IV tPA use (categorical), and NIHSS score upon admission (continuous). Statistical analysis was performed using IBM SPSS statistical software.

3. Results

A total of 571 mechanical thrombectomy patients from May 2013 to January 2019 composed of 86.16% (492/571) and 13.84% (79/571) from 2 CSC centers from August 2017 to January 2019 were initially gathered. A total of 89 patients received a GpIIb/IIIa inhibitor and MT treated with either angioplasty, angioplasty and stenting, or stenting during the study period (average age 69.25 ± 14.21, 25.84% female) across two-stroke centers. Only patients with mechanical thrombectomy and either Eptifibatide or Tirofiban were included. From the dataset, approximately 75% and 83% of individuals from Eptifibatide and Tirofiban respectively underwent mechanical thrombectomy with a stent and angioplasty. Further specifics on stenting and angioplasty alone are summarized in Table 2. Site of Occlusion in which most of the

Table 2
Interventional Procedure.

	Eptifibatide + MT (N = 53)	Tirofiban + MT (N = 36)
Angioplasty or Stenting		
Angioplasty Alone	6	5
Stenting Alone	4	1
Angioplasty + Stenting	40	30
Occlusion Site		
Middle Cerebral Artery	40	23
Internal Carotid Artery	8	10
Anterior Cerebral Artery	2	0
Posterior Cerebral Artery	2	0
Common Carotid Artery	0	1
Basilar Artery	1	1
Vertebral Artery	0	1

procedures took place for both cohorts is the middle cerebral artery. Out of the 89 patients, 40.45% (36/89) were treated with Tirofiban + MT (average age 69.25 ± 14.18, 27.78% female) and 59.55% (53/89) were treated with Eptifibatide + MT (average age 69.25 ± 14.36, 24.53%). Baseline demographics, risk factors, and outcomes are summarized in Table 3.

The IV tPA use did show a statistical difference between the two groups (p = .01). Reperfusion was successful (TICI 2b/3) in 94.44% of Tirofiban + MT cases compared to 92.16% of Eptifibatide + MT cases (p = .678). NIHSS scale upon admission for Eptifibatide + MT patients (average NIHSS score 14.55 ± 8.599) compared to Tirofiban + MT (average NIHSS score 13.08 ± 9.057) (p = .441). Four patients (11.11%) in the Tirofiban + MT group had symptomatic hemorrhage versus four patients (7.55%) in the Eptifibatide + MT (p = .564). The mortality rate at discharge did not show a statistical difference between the two groups (p = .573). Good clinical outcome at discharge (mRS ≤ 2) was achieved in 35.85% of Eptifibatide + MT patients and 30.56% of Tirofiban + MT patients (p = .604). Things to consider on the rate of good outcomes at discharge is that we routinely treat patients with mRS of 3 at baseline with LVO and significant change in functional ability, we also were treating more patients in the later time windows during and after the DAWN and DEFUSE 3 trials.

Results of the univariate analysis for baseline characteristics, IV tPA use, and clinical outcomes are summarized in Table 1. IV tPA use demonstrated a statistically significant difference between Eptifibatide + MT and Tirofiban + MT groups. All other variables did not show a strong trend towards a significant difference (P > .05) and, therefore, were not included in the multivariate analysis.

Subsequently, a multivariate analysis was conducted with statistically significant variables summarized in Table 4. The odds of symptomatic hemorrhage (OR 0.729, 95% CI 0.155–3.440), the mortality rate at discharge (OR 1.288, 95% CI 0.406–4.088), the good outcome at discharge (OR 1.364, 95% CI 0.490–3.798), and good TICI score (OR 0.700, 95% CI 0.107–4.564) showed no statistically significant difference between the two groups.

Table 3
Univariate analysis evaluating baseline variables, procedural characteristics and outcomes.

Overall Number (%)	Eptifibatide + MT (N = 53)	Tirofiban + MT (N = 36)	P value
Age (mean ± SD)	69.25 ± 14.36	69.25 ± 14.18	0.406
Gender			0.620
Men	40 (75.47)	26 (72.22)	
Women	13 (24.53)	10 (27.78)	
Race/ethnicity			0.214
Hispanic	39 (73.58)	22 (61.11)	
White	14 (26.42)	14 (38.89)	
Co-morbid conditions			
Hypertension	47 (88.68)	28 (77.77)	0.165
Diabetes Mellitus	26 (49.06)	14 (38.89)	0.344
Atrial fibrillation	15 (28.3)	3 (8.33)	0.021
Cigarette smoking	11 (20.75)	5 (13.88)	0.407
Coronary artery disease	10 (18.68)	7 (19.44)	0.949
Congestive heart failure	6 (11.32)	5 (13.89)	0.719
In-hospital complication			
Intracerebral hemorrhage (symptomatic hemorrhage)	4 (7.55)	4 (11.11)	0.564
Thrombolysis in cerebral infarction			
Good (post TICI score 2b-3)	47 (92.16)	34 (94.44)	0.678
Outcome (mean ± SD)	3.358 ± 2.058	3.611 ± 1.793	0.5507
Good (mRS discharge score 0–2)	19 (35.85)	11 (30.56)	0.604
Mortality at Discharge	13 (24.53)	7 (19.44)	0.573
IV tPA use	20 (37.74)	5 (13.89)	0.01
NIHSS upon admission	14.55 ± 8.599	13.08 ± 9.057	0.441

Table 4
Multivariate analysis evaluating effect of Tirofiban on outcomes of acute ischemic stroke patients who underwent endovascular treatment.

Outcomes	Unadjusted		Adjusted for Afib, IV tPA and NIHSS	
	OR (95% CI)	P value	OR (95% CI)	P value
Symptomatic Hemorrhage	0.653 (0.152–2.8)	0.564	0.729 (0.155–3.440)	0.690
Mortality Rate at Discharge	1.346 (0.478–3.793)	0.573	1.288 (0.406–4.088)	0.667
Good outcome at discharge (mRS score 0–2)	1.270 (0.514–3.138)	0.604	1.364 (0.490–3.798)	0.553
Good TICI score (2b-3)	0.691 (0.120–3.993)	0.678	0.700 (0.107–4.564)	0.709

4. Discussion

The analysis of acute ischemic stroke patients treated with mechanical thrombectomy and acute stenting while treated with Tirofiban showed no significant difference compared to those patients treated with Eptifibatide. There was no difference in symptomatic hemorrhage rates, mortality at discharge, discharge mRS scores, and TICI scores between the two groups. The multivariate analysis respectively for Eptifibatide + MT and Tirofiban + MT cohorts: symptomatic hemorrhage rates 7.55% and 11.11% (p = .564), mortality rates 24.53% and 19.44% (p = .573), rate of good clinical outcome (mRS dc 0–2) 35.85% and 30.56% (p = .604), and TICI score 2b-3 rates are 92.16% and 94.44% (p = .678). Tirofiban and MT in patients with underlying intracranial atherosclerosis show no difference in the variables studied when compared to Eptifibatide.

Our study shows a similarly favorable outcome of mechanical thrombectomy and acute stenting following IV infusion of tirofiban with similar sICH rates, mortality rates, and favorable outcome rates with the Eptifibatide cohort a well-established glycoprotein IIB/IIIA inhibitor. Although there has been data on Tirofiban application in coronary artery disease and intracranial aneurysms, there has been a lack of evidence in the safety and efficacy of Tirofiban in conjunction with mechanical thrombectomy of intracranial disease. Eptifibatide has been used in the clinical treatment setting longer than Tirofiban, but recently there has been a push for Tirofiban's use in conjunction with mechanical thrombectomy. Our study aids in the evidence of pushing for Tirofiban in conjunction with mechanical thrombectomy when acute stenting is needed.

Placement of stents require antiplatelet therapy, which can potentially increase the risk of intracranial hemorrhages. In our study, Tirofiban and Eptifibatide groups exhibited an 11.11% and 7.55% intracerebral hemorrhage rates post-intervention which are lower than intracerebral hemorrhage rates of 18% in a cohort of mechanical thrombectomy with tandem lesions [10]. Bleeding complications in our series did not show higher hemorrhagic rates These results are comparable with data of retrospective studies of 141 and 19 patients treated with endovascular therapy involving stenting and Tirofiban, which showed hemorrhagic rates of 15.7% and 8.8% [11,12]. The rate of Tirofiban + MT is 11.11% was relatively similar to a comparative study of AIS patients who underwent mechanical without Tirofiban of 10.2%, [13] but also similar to hemorrhage rate of mechanical thrombectomy with Tirofiban of 10.6% [13]. However, in the study by Kellert et al., they reported higher rates of symptomatic intracerebral hemorrhage in stroke patients receiving intravenous tirofiban [14]. Several factors can account for the high sICH such as patients had a higher NIHSS upon admission of roughly 18, which is higher than Tirofiban + MT patients in our study was 13, and more than ten different devices were used in the mechanical thrombectomy cases analyzed, which could lead to the high number of sICH. Despite these results, our study shows that IV

administration of Tirofiban is as effective and safe as a prevalently used glycoprotein IIB/IIA inhibitor (Eptifibatide).

The average NIHSS mean for Eptifibatide and Tirofiban cohort respectively were 14.55 ± 8.599 and 13.08 ± 9.057, which are better than the tandem cohort consisting of 17.6 ± 5.0 [10]. Furthermore, our analysis had TICI scores 2b-3 rates better than the tandem lesion group TICI scores. Cureus et al. reported a 100% TICI score of 2b-3 in a cohort size of 6 administered with glycoprotein IIB/IIIa inhibitor for large vessel occlusion [15]. Favorable post-TICI score was significantly higher than patients without an antiplatelet therapy in large multicenter retrospective analysis [16]. Additionally, the rate of a good outcome was measured at discharge and not followed up at 90 days since approximately 40% of patients did not come back for follow and, therefore, unable to provide data regarding post-discharge.

The negligible differences in safety and effectiveness could be a result of contrary chemical structures. For example, Tirofiban is half the molecular weight of Eptifibatide [3–5]. Based on a study regarding glycoproteins chemical structures, Eptifibatide is a synthetic cyclic heptapeptide with cysteine bridges, while Tirofiban is a small, non-peptide, tyrosine-like peptidomimetic [3–5]. As well as, Tirofiban has a higher specificity and affinity for glycoprotein IIb and IIIa receptors allowing it not to dissociate as fast as Eptifibatide [3–5]. Despite these differences, both glycoproteins have very similar safety and effectiveness when treating underlying intracranial atherosclerosis. Another reason Tirofiban can be more effective is that it "dissociates from the receptor at a half-life of 11 s," which is faster than Eptifibatide: furthermore: Tirofiban has a shorter half-life allowing its antiplatelet effect to seize as soon as infusion halts [3,4,17].

Specific limitations of our study must be taken into consideration. First, the study was conducted retrospectively and contained non-standardized treatment. Second, the small sample size is a limitation. Furthermore, interventional teams have gained experience using glycoproteins inhibitors, which affected surgeries in the earlier period. Third, between 2016 and 2017, there was an inclusion of wake-up strokes due to the DAWN trial, which affected the data during that time frame. Lastly, our data, compared to many other studies did not have any inclusion or exclusion criteria. However, these limitations do not significantly influence the principal results.

5. Conclusion

In conclusion, mechanical thrombectomy and acute stenting with Tirofiban does not intensify the risk of hemorrhage or mortality compared to Eptifibatide. There was no statistically significant difference in symptomatic hemorrhage, mortality rates, and discharge outcomes demonstrating the equivalent effectiveness/safety. Tirofiban provides an alternative agent in conjunction with mechanical thrombectomy and acute stenting. More extensive studies are warranted to prove the safety and efficacy of Tirofiban compared to Eptifibatide in acute ischemic stroke patients treated with mechanical thrombectomy and acute stenting.

Author contributions

AH provided research question, analyzed the data, and revised the paper. HM developed the statistical analyses, drafted the paper, and revised the paper. RR analyzed the data and revised the paper. LP monitored development of database and navigated endovascular database. AG analyzed data. HK revised the paper.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement

Datasets are available on request.

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