Journal of Interventional Medicine 3 (2020) 174–179

HOSTED BY

Contents lists available at ScienceDirect

Journal of Interventional Medicine

journal homepage: www.keaipublishing.com/cn/journals/journal-of-interventional-medicine/

Effects of two different glycoprotein platelet IIb/IIIa inhibitors and the clinical endpoints in patients with intracranial Pipeline flow diverter implant

Qiao Deng, Shichao Zhang, Mingzhou Li, Guozhong Zhang, Wenfeng Feng *

Southern Medical University, Department of Neurosurgery, Nanfang Hospital, Guangzhou, 510515, China

ARTICLE INFO

Keywords:
Eptifibatide
Tirofiban
Cerebral hemorrhage
Flow guiding device

ABSTRACT

Objective: To compare the antiplatelet effect and major adverse cerebrovascular events of Pipeline for intracranial aneurysms using glycoprotein IIb/IIIa antagonists (GPI) eptifibatide and tirofiban.

Methods: Retrospective analysis of relevant data of patients using GPIs combined with oral antiplatelet therapy in Nanfang Hospital of Southern Medical University from December 2017 to December 2019. The study was approved by the ethics Committee of Nanfang Hospital of Southern Medical University. According to the random use of GPIs drugs, they were assigned to the eptifibatide group and tirofiban group. Basic data, platelet inhibition rates at baseline, 24h and 72h after administration, short-term major adverse cerebrovascular events, and bleeding complications were compared between the two groups.

Results: A total of 47 patients were included in this study, including 24 patients in eptifibatide group and 23 patients in tirofiban group. There was no significant difference in average age (53.75 *vs.* 53.91 years) and body mass index (BMI) (24.39 *vs.* 22.73 kg/m2) between eptifibatide group and tirofiban group. There was no significant difference in coagulation factor function (R), fibrinogen function (K), fibrinolysis function (EPL), comprehensive coagulation index (Cl), arachidonic acid pathway inhibition rate (AA%) and adenosine diphosphate inhibition rate (ADP%). However, the baseline level of residual platelet function MA (ADP) in eptifibatide group was significantly higher than that in tirofiban group (50.79 *vs.* 35.29 mm, $P = 0.0026$). There was a statistical difference in the platelet aggregation function MA (65.38 *vs.* 62.54 mm, $p = 0.0442$), the rate of spontaneous hemorrhagic stroke (4.3% *vs.* 0%) and the rate of asymptomatic minor bleeding (26.08% *vs.* 4.1%) in the two groups ($P < 0.05$).

Conclusion: Both eptifibatide and tirofiban can effectively inhibit platelets, but the effect of etifeptide is better than that of tirofiban in preventing intracranial microhemorrhage and asymptomatic cerebral infarction.

Introduction

Effective platelet suppression is one of the important medical interventions to prevent ischemic complications during endovascular interventional procedures and after stent implantation. Although conventional oral antiplatelet drugs can provide stable and effective platelet inhibition, more rapid administration of intravenous antiplatelet drugs are often required during endovascular stent placement or acute stroke. Glycoprotein Platelet IIb/IIIa Inhibitors (GPIs) administered through a short continuous intravenous infusion have been proven to be safe and effective.[1,2] GPIs currently in clinical use include abciximab, eptifibatide, and tirofiban, all of which can disrupt acute platelet-mediated thrombosis; however, differences in stroke outcomes have been observed among different GPIs. Previously, some foreign meta-analyses have compared the effectiveness and safety of abciximab and eptifibatide in percutaneous coronary intervention.[3] Due to the long half-life and low clinical use of abciximab, tirofiban and eptifibatide antiplatelet therapy are mainly used in intravascular interventions in China. The eptifibatide effect is directly proportional to plasma concentration, with a half-life of 2–4 h, and platelet function returns to normal within 4–8 h after discontinuation.[4] So far, the differences in platelet inhibitory effects and in the appropriate dosage regimens have not been clarified. Thrombus-related complications after the implantation of Pipeline flow device are still common,[5–7] and the use of standardized and individualized GPIs during a short-term intravenous operation is particularly important.[8] The purpose of this study was to compare the antiplatelet

* Corresponding author. Department of Neurosurgery, Nanfang Hospital, Southern Medical University, Guangzhou, 510515, China.
E-mail address: 905528697@qq.com (W. Feng).

https://doi.org/10.1016/j.jimed.2020.08.005
Received 12 April 2020; Received in revised form 11 July 2020; Accepted 3 August 2020
Available online 16 August 2020

effects of eptifibatide and tirofiban and the incidence of major adverse cerebrovascular events after treatment of intracranial aneurysms with the Pipeline flow diverter. The results of this study would provide guidance for clinically relevant treatments to reduce complications associated with Pipeline implant.

Patients and methods

Patients

We retrospectively analyzed patients in the Department of Neurosurgery, Nanfang Hospital of Southern Medical University, who underwent GPI antiplatelet therapy after the treatment of intracranial aneurysms with the implantation of Pipeline flow diverter from December 2017 to December 2019. This study was approved by the Medical Ethics Committee of Nanfang Hospital of Southern Medical University, and the patients signed the informed consent forms. We included patients with moderate and large unruptured aneurysms in the internal carotid artery, multiple small aneurysms, and relapsed refractory aneurysms that required a single Pipeline flow diverter treatment.

Clinical study procedures

According to the use of GPIs after the implantation of Pipeline flow diverter, the patients were assigned to the eptifibatide group and the tirofiban group. Patients in the eptifibatide group received the first dose (180 μg/kg) intravenously immediately after the operation, followed by a continuous intravenous drip of 2.0 μg/kg/min or 3–6 ml/h. The first bolus of the tirofiban group was 10 μg/kg, followed by intravenous infusion at 0.15 μg/(kg.min). Venous blood samples were collected for examination at baseline (before administration), 24 h, and 72 h after administration. The blood collection interval was based on the first intravenous administration of GPIs and is not affected by the law of natural time. Thromboelastography (TEG) was used to determine the coagulation factor function (R), fibrinogen function (K), fibrinolysis function (EPL), platelet aggregation function (MA), comprehensive coagulation index (Cl), arachidonic acid pathway inhibition rate (AA %), adenosine diphosphate inhibition rate (ADP %), and platelet activity after the administration of the GPIs. During the perioperative period, the total duration of controlling the use of eptifibatide and tirofiban was 12 h from the first intravenous administration. Additionally, in order to acquire adequate protection against thrombosis, all patients receiving the Pipeline flow diverter received at least 100 mg/d aspirin and 75 mg/d clopidogrel 3 days before surgery. Heparin was neutralized in both groups of patients immediately after the operation, and they took antiplatelet drugs for at least 6 months.

Safety assessments

The main safety endpoints were bleeding events and cerebrovascular events (death, hemorrhagic stroke, ischemic stroke, delayed cerebral ischemia, or the need for target vascular reconstruction). Bleeding events included intraoperative and perioperative events, and perioperative events were defined as the events that occurred within 48 h after the implantation of pipeline. Secondary safety endpoints included asymptomatic intracerebral hemorrhage and thrombotic-related events. Massive bleeding included central nervous system, retroperitoneal bleeding, gastrointestinal bleeding, or at least 1 unit of red blood cell input during hospitalization. Minor bleeding included hematoma at the puncture site, ecchymosis of the skin in the groin area, and bleeding gums or mucosal bleeding.

Statistical analyses

Statistical analyses were performed using SPSS (V.25.0; IBM Corporation, Armonk, New York, USA). Normally distributed variables are presented as mean ± SD, and other data as median and interquartile range, if not specified otherwise. Multivariate logistic regression model was used to assess the relationship between bleeding and cerebrovascular events, which was adjusted based on baseline characteristics (including hypertension, diabetes, target vessel diameter, and use of clopidogrel or ticagrelor).

Results

Subjects

Of the 47 subjects who were recruited and treated in this study, 24 people were in the eptifibatide group and 23 people were in the tirofiban group. Comparing both groups, there were no statistical difference in the average age of the patients (53.75 *vs.* 53.91 years), body mass index (24.39 *vs.* 22.73 kg/m^2), gender, history of thromboembolism, smoking, hypertension, hyperlipidemia, and diabetes, and preoperative platelet counts. Similarly, no statistically significant difference was found in platelet function measured at baseline; however, baseline levels of residual platelet function were higher in the eptifibatide group than in the tirofiban group (50.79 *vs.* 35.29 mm, $p = 0.0026$). No statistical difference in MA (ADP) which are refers to residual platelet activity after changing ADP pathway inhibitors (Fig. 1).

Comparison of platelet function

The results of TEG at 24 h and 72 h postoperatively in the two groups showed no statistical differences in R, K, EPL, Cl, AA %, ADP %, and MA (ADP) levels. There was a significant difference in MA (65.38 *vs.* 62.54 mm, $p = 0.0442$) at 24 h after administration. Intravenous infusion of eptifibatide or tirofiban was stopped 72 h after administration, and there was no statistical difference in MA (show Fig. 2) (see Fig. 3).

Complications

There were significant differences in spontaneous hemorrhagic stroke rate (4.3% *vs.* 0%) and asymptomatic mild hemorrhage rate (26.08% *vs.* 4.1%) between the two groups. Of the patients in the tirofiban group, 30.38% had cerebral hematoma unrelated to surgery, microhemorrhage, or other forms of bleeding (such as puncture point bleeding and gingival bleeding) during hospitalization and observation. There was no difference between the two groups with regard to major thrombus-related events during hospitalization (13% *vs.* 8.3%). Two patients had acute thrombosis and three patients had acute cerebral infarction in the cerebral hemisphere. No serious thrombotic complications occurred in all the patients. The modified Rankin score and neurological deficit score were 0–1 at discharge.

Discussion

The platelet GP IIb-IIIa antagonists, eptifibatide and tirofiban, can prevent death or myocardial infarctions in patients with cerebrovascular interventional operation and percutaneous coronary intervention.[9–11] There are currently no randomized clinical trials or published guidelines to support antiplatelet therapy regimens or duration after Pipeline implantation in specific blood vessels.[12,13] Compared with antiplatelet drugs, such as heparin and aspirin, the dose-response relationship and appropriate dose regimen of GPI have not been systematically evaluated. Although there is evidence that GPIs are safe and effective in reducing cerebral ischemic events in nerve interventional therapy, there is little comparative data to help clinicians determine which drugs are associated with the best clinical outcome. The increasing risk of cerebral hemorrhage without additional clinical benefits has affected the use of GPI,[14,15] and finding a balance that minimizes the risk of thrombosis and hemorrhage is fundamental.[16] Compared with tirofiban, eptifibatide has the disadvantages of relatively higher price, shorter clinical application time,

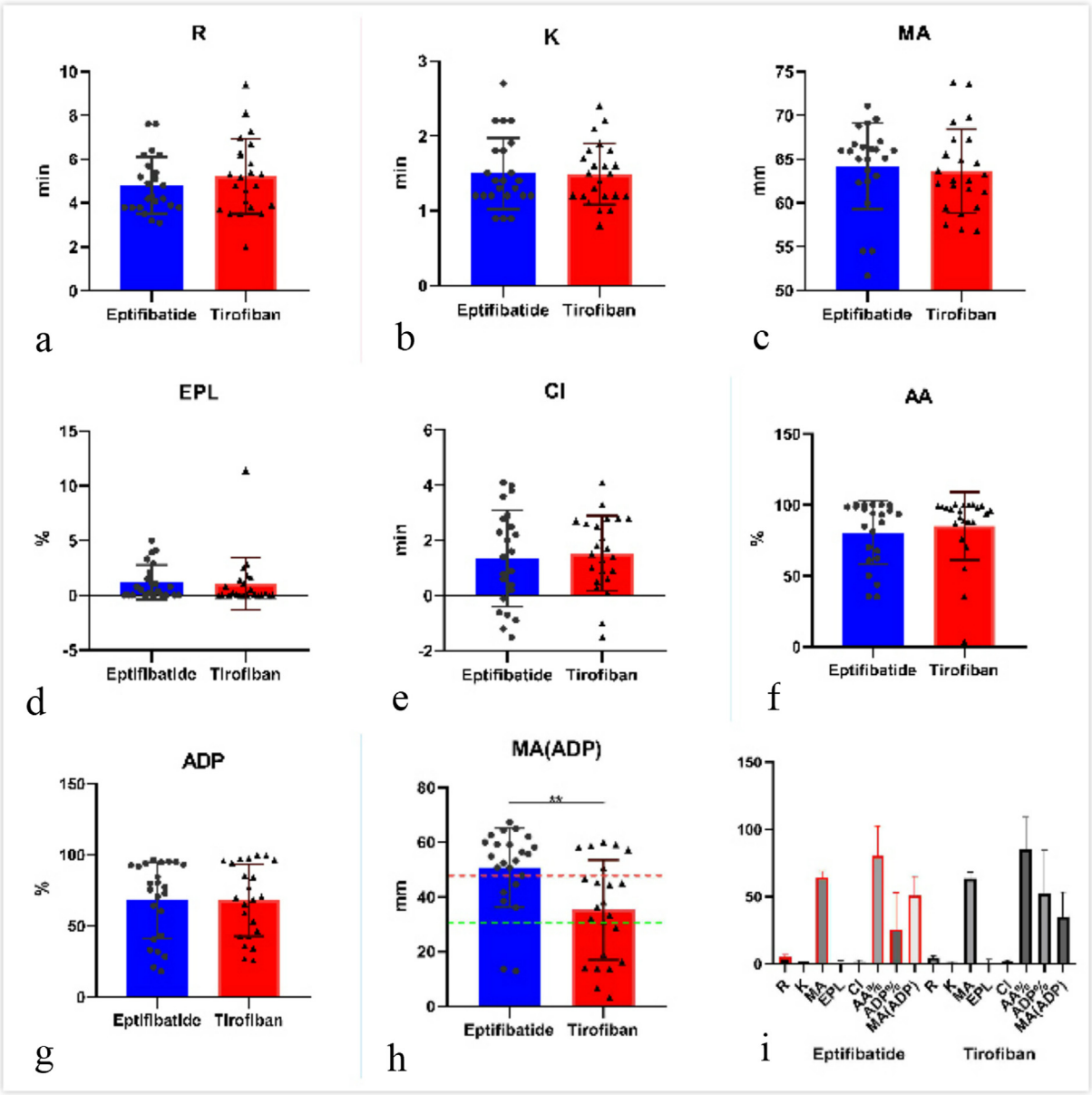

Fig. 1. Comparison of baseline levels between eptifibatide and tirofiban. (a–b): difference in coagulation factor function and fibrinogen function; (c–d): difference in fibrinolysis function and platelet aggregation function; (e): change in comprehensive coagulation index; (f): degree of inhibition rate of arachidonic acid pathway; (g): degree of inhibition rate of adenosine diphosphate; (h): comparison of residual platelet activity between the two groups after drug use; (i): summary of data in the two groups of patients.

and less popularity. The pharmacokinetics of eptifibatide are linear for bolus doses ranging from 90 to 250 mg/kg and infusion rates ranging from 0.5 to 3 mg/kg/min.[17–19] Eptifibatide is not metabolized by cytochrome P450, but by deaminate metabolic enzymes, and the majority of the metabolites are deaminated and polar metabolites.

The Pipeline flow diverter is more widely used in middle cerebral artery and anterior cerebral small fusiform or saccular aneurysms. Although it is currently an effective treatment, the risk of thromboembolism (14%) and hemorrhagic complications (11%) associated with stent therapy still need to be addressed. Michelozzi et al., reported that 35 cortical branches were covered in 30 patients with middle bifurcation aneurysms treated with a Pipeline flow diverter, and regular intraoperative use of GIs improved asymptomatic and symptomatic ischemic events in the perforator area.[20]

In this study, we have discussed the safety of eptifibatide in the treatment of nerve intervention and compared its therapeutic effect with that of tirofiban. TEG was used to detect the platelet inhibition rate at baseline (before administration), 24 h, and 72 h after administration. We analyzed the short-term major adverse cerebrovascular events and bleeding complications in patients with eptifibatide and tirofiban to explore the therapeutic advantages of these two types of GPI. We found that intravenous administration of GPI affected the platelet function of the patients, which decreased from the baseline value after 24 h of drug withdrawal. At 24 h after operation, the decrease in the tirofiban group was greater than that in the eptifibatide group. There was a significant difference in platelet aggregation function between the two groups (65.38 *vs.* 62.54 mm, $p = 0.0442$). For patients with obvious inhibition of MA, the amount of blood oozing in the operating field was significantly more than that in normal patients during the necessary craniotomy, and tirofiban may have a stronger effect on MA, which may be related to low probability of intracranial hemorrhage. In addition, the adjuvant application of tirofiban in progressive stroke, intravenous thrombolysis, and

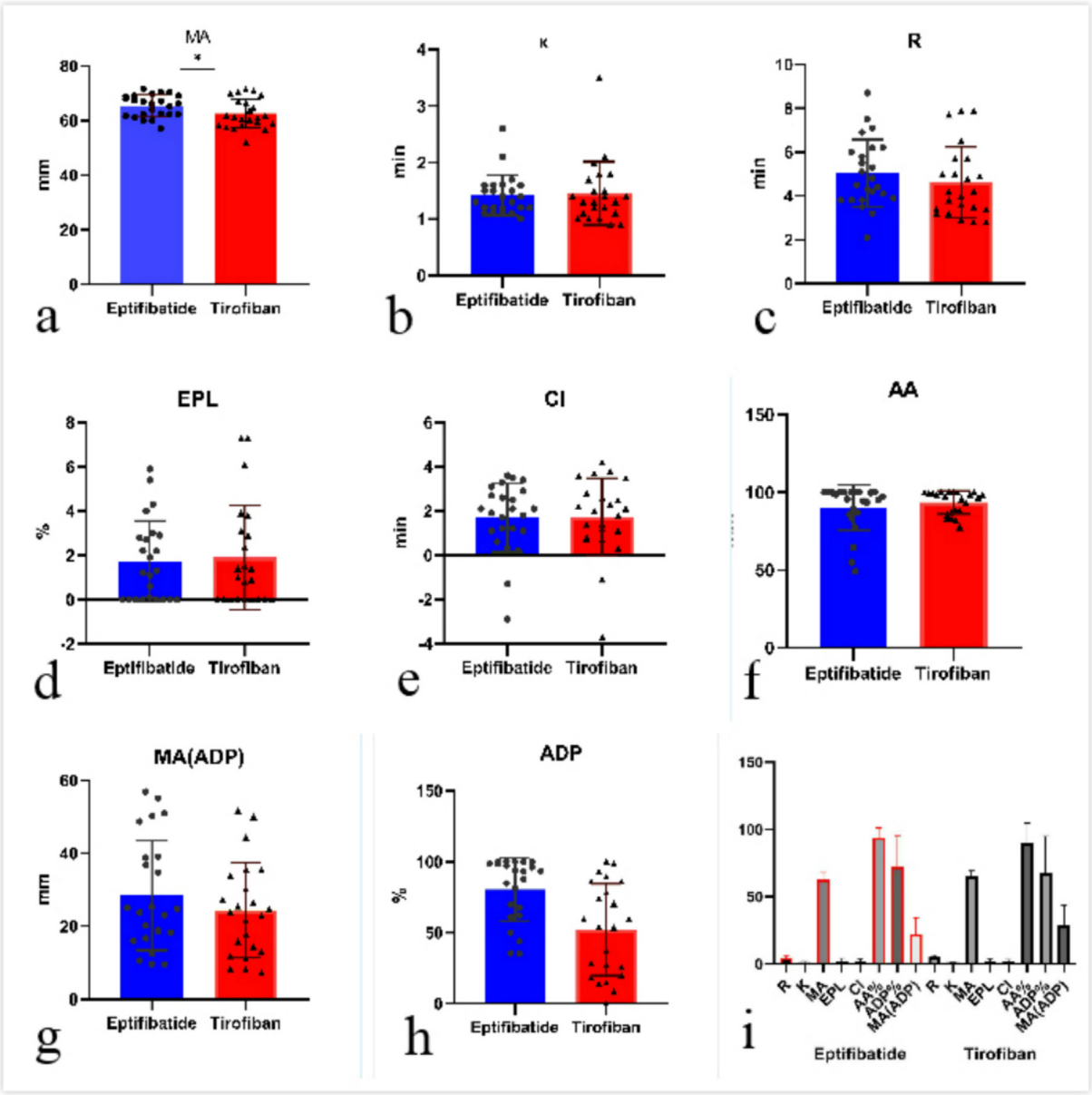

Fig. 2. Comparison of platelet function between the two groups at 24 h after operation. (a–b): difference in fibrinolysis function and fibrinogen function; (c–d): difference in coagulation factor function and platelet aggregation function; (e): change in comprehensive coagulation index; (f): degree of inhibition rate of arachidonic acid pathway; (g): degree of inhibition rate of adenosine diphosphate; (h): comparison of residual platelet activity between the two groups after drug use; (i): summary of data in the two groups of patients.

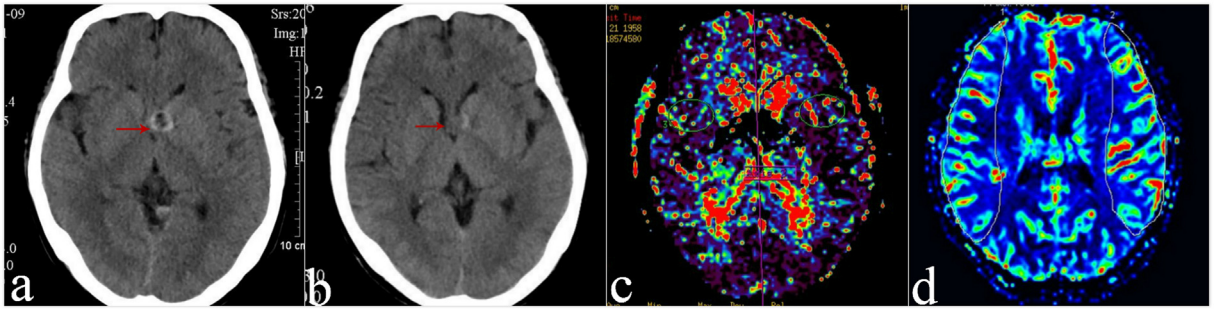

Fig. 3. Imaging results of plain cranial scan and perfusion CT in a patient with minimal intracranial hemorrhage. (a): 24 h after operation, CT suggested that the left basal ganglia was removed; (b):72 h later, CT showed that the area of microcircular hemorrhage was less than that before; (c–d): perfusion CT suggested that there was no significant difference in mean blood perfusion between the two hemispheres.

endovascular therapy has been widely evaluated, and it is well tolerated and effective in improving vascular recanalization and long-term functional outcome. However, its optimal dose, scope of application, and accurate target have not been determined, and hence, its overuse can cause serious hemorrhagic stroke events.[21,22] Gunase et al., reported a slight statistically significant increase in small bleeding and massive bleeding in a high-dose tirofiban group, which required blood transfusion.[23] Schiariti et al., conducted trials to compare the effects of high-dose tirofiban and eptifibatide, and antiplatelet regimen with the incidence of compound ischemic events were the main end points within 1 year. They reported ischemic events in 65 cases, with 47 cases in the tirofiban group and 18 cases in the eptifibatide group in (9.1% *vs.* 12.2%, $p = 0.22$).[24] Lewis et al., showed that the 24-h platelet inhibition level of patients treated with abciximab was significantly higher than that of patients treated with eptifibatide ($p < 0.001$) and tirofiban ($p < 0.05$). There was no significant difference in platelet inhibition between the eptifibatide group and the tirofiban group.[25]

Conclusions

Our study is the first to explore the inhibition of platelet function and the difference between eptifibatide and tirofiban with regard to cerebrovascular events after the implantation of Pipeline flow diverter. The findings of this study suggest that tirofiban had a negative effect on MA and MA (ADP), and the incidence of adverse cerebrovascular events increased slightly. We also found that the safety of eptifibatide in nerve interventional therapy is slightly higher than that of tirofiban, and eptifibatide has a certain therapeutic advantage in the prevention of asymptomatic intracranial microhemorrhage. In general, eptifibatide is safe and effective in preventing acute thrombosis associated with the implantation of intracranial Pipeline flow diverter and well tolerated in healthy people. The limitations of this study include the lack of molecular mechanism experiments, poor factor controllability, and lack of baseline uniformity. In addition, we hope that future studies would involve larger sample size of patients for better analysis of the differences and effects of GPIs.

Declaration of competing interest

The authors declare that they have no conflicts of interests to this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Abbreviations

ADP%	adenosine diphosphate inhibition rate
AA%	arachidonic acid pathway inhibition rate
EPL	fibrinolysis function
GPI	glycoprotein IIb/IIIa antagonist
MA (ADP)	residual platelet function after changing ADP pathway inhibitors
MA	platelet aggregation function
TEG	thrombela-stogram

Availability of data and material

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

Ethics approval

The study was approved by the ethics committee of Nanfang Hospital of Southern Medical University. All clinical practices and observations were conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each patient before the study was conducted.

Patient consent

Written informed consent was obtained from patients for publication of these case reports and any accompanying images.

Funding

None.

Authors' contributions

DQ wrote the manuscript. WF managed patient care and edited the manuscript. All authors read and approved the final manuscript.

Consent for publication

The patients provided written informed consent before undergoing endovascular surgery and related clinical data collection.

References

1. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378:708–718.
2. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20.
3. Cagnazzo F, Mantilla D, Lefevre PH, et al. Treatment of middle cerebral artery aneurysms with flow-diverter stents: a systematic review and meta-analysis. *AJNR*. 2017;38:2289–2294.
4. Pancioli AM, Adeoye O, Schmit PA, et al. Combined approach to lysis utilizing eptifibatide and recombinant tissue plasminogen activator in acute ischemic stroke-enhanced regimen stroke trial. *Stroke*. 2013;44:2381–2387.
5. Adeeb N, Griessenauer CJ, Foreman PM, et al. Use of platelet function testing before pipeline embolization device placement: a multicenter cohort study. *Stroke*. 2017;48:1322–1330.
6. Texakalidis P, Bekelis K, Atallah E, et al. Flow diversion with the pipeline embolization device forpatients with intracranial aneurysms and antiplatelet therapy: a systematic literature review. *Clin Neurol Neurosurg*. 2017;161:78–87.
7. Ocal O, Peker A, Balci S. Placement of a stent within a flow diverter improves aneurysm occlusion rates. *AJNR*. 2019;40:1932–1938.
8. Michelozzi, Caterina, Darcourt, et al. Flow diversion treatment of complex bifurcation aneurysms beyond the circle of Willis: complications, aneurysm sac occlusion, reabsorption, recurrence, and jailed branch modification at follow-up. *Neurosurgery*. 2019;131:1751–1762.
9. Velibey Y, Guvenc TS, Demir K, et al. Effects of bailout tirofiban on in-hospital outcomes and long-term mortality in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous intervention. *Angiology*. 2019;70:431–439.
10. Lapostolle F, Van't Hof AW, Hamm CW, et al. ATLANTIC Investigators. Morphine and ticagrelor interaction in primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: ATLANTIC-morphine. *Am J Cardiovasc Drugs*. 2019;19:173–183.
11. Wallentin L, Becker RC, Budaj A, et al. PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057.
12. Valgimigli M, Biondi-Zoccai G, Tebaldi M, et al. Tirofiban as adjunctive therapy for acute coronary syndromes and percutaneous coronary intervention: a meta-analysis of randomized trials. *Eur Heart J*. 2010;31:35–49.
13. Dannenberg L, Wolff G, Naguib D, et al. Safety and efficacy of tirofiban in STEMI-patients. *Int J Cardiol*. 2019;274:35–39.
14. Goyal M, Demchuk AM, Menon BK, et al. Andomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372:1019–1030.
15. Rossen JD, Chalouhi N, Wassef SN, et al. Incidence of cerebral ischemic events after discontinuation of clopidogrel in patients with intracranial aneurysms treated with stent-assisted techniques. *J Neurosurg*. 2012;117:929–933.
16. Valgimigli M, Gagnor A, Calabro P, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet*. 2015;385:2465–2476.
17. Seners P, Hurford R, Tisserand M, et al. Is unexplained early neurological deterioration after intravenous thrombolysis associated with thrombus extension]. *Stroke*. 2017;48:348–352.
18. Wu C, Sun C, Wang L, et al. Low-dose tirofiban treatment improves neurological deterioration outcome after intravenous thrombolysis. *Stroke*. 2019;50:3481–3487.
19. Amsterdam EA, Wenger NK, Brindis RG, et al. AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228.
20. Michelozzi C, Darcourt J, Guenego A, et al. Flow diversion treatment of complex bifurcation aneurysms beyond the circle of Willis: complications, aneurysm sac occlusion, reabsorption, recurrence, and jailed branch modification at follow-up. *J Neurosurg*. 2019;131:1751–1762.

21. Kim JS, Han DC, Jeong YH, et al. Antiplatelet effect of ticagrelor compared to tirofiban in non-ST-segment elevation ACS patients undergoing PCI: the result of the TE-CLOT trial. *Thromb Haemostasis*. 2016;115:213–221.
22. Fung AY, Saw J, Starovoytov A, et al. Abbreviated infusion of eptifibatide after successful coronary intervention. The BRIEF-PCI (brief infusion of eptifibatide following percutaneous coronary intervention) randomized trial. *J Am Coll Cardiol*. 2009;53:837–845.
23. Gascou G, Lobotesis K, Brunel H, et al. Extra-aneurysmal flow modification following pipeline embolization device implantation: focus on regional branches, perforators, and the parent vessel. *Am J Neuroradiol*. 2015;36:725–731.
24. Schiariti M, Saladini A, Cuturello D, et al. Long-term efficacy of high-dose tirofiban versus double-bolus eptifibatide in patients undergoing percutaneous coronary intervention. *J Cardiovasc Med*. 2011;12:29–36.
25. Holmes LE, Gupta R, Rajendran S, et al. A randomized trial assessing the impact of three different glycoprotein IIb/IIIa antagonists on glycoprotein IIb/IIIa platelet receptor inhibition and clinical endpoints in patients with acute coronary syndromes. *Cardiovasc Ther*. 2016;34:330–336.