Online February 25, 2021
Journal of Neuroendovascular Therapy 2021; 15: 646–652 DOI: 10.5797/jnet.oa.2020-0173

Original Article

Initial Report of the Perioperative Platelet Aggregation Test Using Hematracer ZEN in Neuroendovascular Therapy

Shotaro Ogawa, Daisuke Sato, Fukutaro Ohgaki, Seiei Torazawa, So Fujimoto, Hiroshi Saito, Takeya Suzuki, and Takahiro Ota

Objective: We report the characteristics of the platelet aggregation test using Hematracer ZEN (HTZ; DS medical, Tokyo, Japan) during the perioperative period.

Methods: Among patients undergoing neuroendovascular treatment (EVT) at our hospital between June 2019 and June 2020, 42 consecutive patients with preoperative dual antiplatelet therapy (DAPT) were included. Oral administration of aspirin (ASA) at 81 mg and clopidogrel (CLP) at 75 mg was started 7 days before treatment (Flow Diverter [FD]: 14 days before). We evaluated platelet aggregation activity the day before treatment (FD: 2 days before) using HTZ. We adjusted the CLP dose according to the platelet aggregation test in each patient. We evaluated the platelet aggregating activity after EVT in patients requiring an intracranial stent or in which CLP was adjusted before EVT.

Results: Platelet aggregating activity was able to be evaluated in all patients. In the preoperative examination, the efficacy of CLP was insufficient in one patient (2.4%), optimal medical effects were confirmed in 16 (38.1%), mildly excessive effects were noted in 10 (23.8%), and highly excessive effects were noted in 15 (35.7%). Reassessment was performed postoperatively in 20 patients. We switched CLP to prasugrel in one patient in which the CLP efficacy was considered insufficient in the preoperative evaluation. We reduced the CLP dose in seven patients with marked overdose, and the optimum range was reached in all. We did not adjust the CLP dose in 12 patients judged to have optimal or mildly excessive effects preoperatively, but 4 exhibited highly excessive drug efficacy and required CLP reduction. No postoperative symptomatic cerebral infarction or intracranial hemorrhage was observed (mean observation period: 11 months, range: 4–16 months).

Conclusion: The platelet aggregation test using HTZ was simple and inexpensive, and was useful for adjusting the dose of antiplatelet drugs, but its utility should be evaluated in more patients.

Keywords ▶ neuroendovascular therapy, platelet aggregation test, clopidogrel, Hematracer ZEN, flow diverter stent

Introduction

During the perioperative period before/after neuroendovascular treatment (EVT), antiplatelet drugs are routinely administered to prevent embolic complications.[1,2] The oral administration of two antiplatelet drugs (dual antiplatelet therapy, DAPT) is started 1–2 weeks before treatment. However, there are individual differences in the inhibitory effects of aspirin (acetylsalicylic acid, ASA) and clopidogrel (CLP), which are frequently used, on platelet function.[3–5]

Hyperresponsiveness to antiplatelet drugs is related to hemorrhagic complications,[6] whereas resistance is related to embolic complications.[7] Thus, a preoperative platelet aggregation test is important. Furthermore, several studies revealed that the drug efficacy gradually becomes excessive after starting oral administration.[8,9] In particular, it is recommended that DAPT be continued for a long period when performing treatment using the Flow Diverter (FD) for large aneurysms. Conducting regular platelet aggregation monitoring is necessary to prevent complications.[10]

Hematracer ZEN (HTZ, DS Medical, Tokyo, Japan) is a new device for evaluating platelet aggregation using the screen filtration pressure (SFP) method. Testing is relatively

Department of Neurosurgery, Tokyo Metropolitan Tama Medical Center, Fuchu, Tokyo, Japan

Received: September 12, 2020; Accepted: December 28, 2020
Corresponding author: Shotaro Ogawa. Department of Neurosurgery, Tokyo Metropolitan Tama Medical Center, 2-8-29, Musasidai, Fuchu, Tokyo 183-8524, Japan
Email: brachiocephalic.t.gm@gmail.com

simple and this method is highly correlated with the light transmission aggregometry (LTA) method,[11,12] but no study has reported its use for the regulation of antiplatelet drugs before/after EVT. We report our initial experience with HTZ for evaluating the efficacy of perioperative antiplatelet therapy before/after EVT.

Materials and Methods

Of patients in whom EVT was performed in our hospital between June 2019 and June 2020, the subjects were 42 consecutive patients in whom DAPT (ASA + CLP) was introduced before treatment. The mean age was 62.4 ± 12.6 years. There were 27 females (64.3%). In all, 14 and 7 patients received statin and eicosapentaenoic acid (EPA) preparations, respectively. Concerning techniques, aneurysm treatment was performed in 30 patients (coil embolization: 12, stent-assisted coil embolization: 7, FD: 10, parent artery occlusion: 1), carotid artery stenting (CAS) for cervical internal carotid artery stenosis was performed in 11 (symptomatic: 2, asymptomatic: 9), and stenting for intracranial internal carotid artery stenosis was performed in 1. To evaluate platelet aggregation activity, HTZ was used in all patients. In Japan, platelet aggregation testing using HTZ is covered by health insurance and all measurements conducted in this study were within the range of health care services covered by health insurance. Prior to this study, its protocol was approved by the ethics review board of our hospital and informed consent was received from all patients. When the efficacy of CLP was considered to be insufficient, the oral administration of prasugrel was adopted through ethical inspection.

Perioperative antithrombotic therapy at our hospital

The oral administration of ASA at 81 mg and CLP at 75 mg was started 7 days before treatment (FD: 14 days before treatment). Platelet aggregation was measured the day before treatment (FD: 2 days before treatment). In patients requiring the continuation of CLP administration, the regimen was regulated as follows based on the results of evaluation: (1) drug efficacy insufficiency: CLP was switched to prasugrel, (2) optimal range, slightly excessive: CLP at 75 mg was continued, and (3) highly excessive: the dose of CLP was reduced to 50 mg or administration of 75 mg immediately after testing for every 2 days. In this study, ASA administration was not altered regardless of the results of preoperative measurement. In patients who underwent intracranial stenting or in whom the dose of CLP was regulated before treatment, platelet aggregation was reassessed after treatment.

In patients in whom stent-free coil embolization or parent artery occlusion was performed, the absence of embolic complications was confirmed and the oral administration of CLP was completed the day after treatment. The oral administration of ASA was continued for 1 month.

Sample collection and measurement methods

Sample collection and measurement were conducted according to the following procedures: (1) Using standard venous blood collection methods, 2 mL of whole peripheral blood was collected and placed in a blood collection tube containing an anticoagulant (3.2% sodium citrate); (2) after remaining at room temperature for 1 hour, the blood sample was divided into four special containers of 200 μL; and (3) respective samples were mixed with 22 μL of solution prepared by diluting a platelet-aggregation-inducing substance into four ranks, respectively, and measurement was conducted. As a platelet-aggregation-inducing substance, collagen ("MCM" collagen H; LMS, Tokyo, Japan) was used for drug efficacy tests of ASA. Four concentrations were established: 2.5, 5, 10, and 20 μg/mL. For drug efficacy tests of CLP, ADP ("MCM" ADP, LMS, Tokyo, Japan) was used. Four concentrations were established: 10, 20, 40, and 80 μM. The heating time was established as 1 minute and the reaction time was 5 minutes.

Evaluation of platelet aggregation activity

Assessment of the G type in 6 grades, platelet aggregatory threshold index (PATI), and aggregation rate was possible with HTZ. In G type 2 or 1 patients, the drug efficacy was evaluated as insufficient. G type 0 or –1 was regarded as being within the optimal range. In this test system, concrete PATI values cannot be calculated in patients with a PATI of >8; therefore, they were classified based on the aggregation rate at a maximum concentration of the platelet-aggregation-inducing substance (aggregation rate at Channel 4). Briefly, when the aggregation rate at Channel 4 ranged from 25 to 49%, the G type was evaluated as –2 (the drug efficacy was evaluated as slightly excessive). When it ranged from 0 to 24%, the G type was evaluated as –3 (the drug efficacy was evaluated as highly excessive) (**Table 1**).

Results

In all 42 patients, a preoperative platelet aggregation test was conducted. In 20, platelet aggregation was reassessed

Table 1 Evaluation of drug effects using G type classification according to PATI and platelet aggregation rate at Channel 4

G type	Drug effects	PATI (CLP)	PATI (ASA)
2	Insufficient	<1.0	<0.2
1	Insufficient	1.0–2.0	0.3–0.5
0	Optimum	2.0–4.0	0.5–1.0
–1	Optimum	4.0–8.0	1.0–2.0
–2	Mild excess	>8.0 (Ch4 <50%)	>2.0 (Ch4 >50%)
–3	High excess	>8.0 (Ch4 <25%)	>2.0 (Ch4 >25%)

ASA: acetylsalicylic acid; CLP: clopidogrel; PATI: platelet aggregatory threshold index

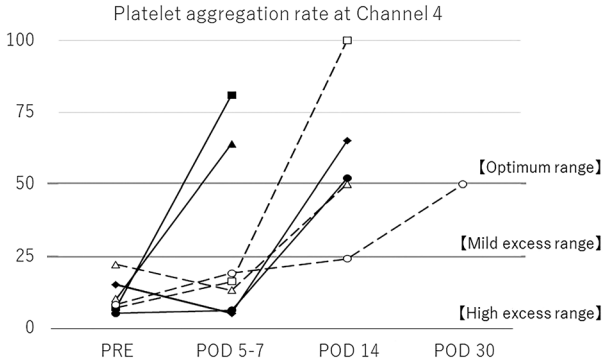

Fig. 1 CLP dose adjustment to the optimal range in patients initially included in the highly excessive range. The CLP dose was reduced to 50 mg and the platelet aggregation ratio reached the optimal range in four patients (solid line).The dose was reduced to 50 mg and then to 50 mg every other day to reach the optimum range in three patients (dotted line). CLP: clopidogrel

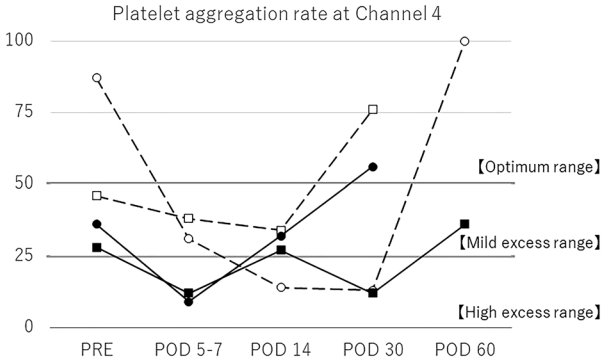

Fig. 2 Delayed conversion to CLP hyperresponsivity and oral dose adjustment to the optimal range. The CLP dose was reduced to 50 mg 5 days after treatment in 2 patients (solid line). The dose was reduced to 50 mg 14 days after treatment in two patients (dotted line). The optimal range was reached in three of four patients. The mildly excessive range was reached in one patient, but no further dose reduction was performed because the risk of stent occlusion was considered to be high. CLP: clopidogrel

after treatment, with a mean frequency of 3.8 times per patient (total: 76 times). Overall, 118 sessions of measurement were possible without problems. The time required for one session of testing involving adjustment of a reagent was ≤1 hour in all patients. Regarding the preoperative test results in the 42 patients, the efficacy of CLP was evaluated as insufficient in 1 (2.4%), being in the optimal range in 16 (38.1%), slightly excessive in 10 (23.8%), and highly excessive in 15 (35.7%). The efficacy of ASA was evaluated as insufficient in 2 (4.8%), being in the optimal range in 23 (54.8%), slightly excessive in 8 (19.0%), and highly excessive in 9 (21.4%).

In one patient in whom the efficacy of CLP was evaluated as insufficient before treatment, CLP administration was discontinued and prasugrel at 20 mg was administered the day before treatment. Oral administration at 3.75 mg/day was continued from the day of treatment. In seven patients in whom the efficacy of CLP was evaluated as highly excessive on preoperative assessment, the dose of CLP was reduced from the day before treatment or the day of treatment, and it was confirmed that the optimal range was reached in all patients (**Fig. 1**).

There was no symptomatic cerebral infarction or intracranial hemorrhage during the postoperative course (mean follow-up period: 11 months, 4–16 months). However, in 4 of 12 patients in whom the drug efficacy was evaluated as optimal or slightly excessive before treatment, the drug efficacy often became excessive, requiring a switch to lower-dose administration after treatment (**Fig. 2**).

Nine patients in the excessive CLP efficacy group (n = 25) and five in the optimal group (n = 16) on pretreatment testing received statin preparations, but there was no significant difference between the two groups ($p = 0.13 > 0.05$). Furthermore, four patients in the former and three in the latter received EPA preparations, but there was no significant difference between the two groups ($p = 1.0 > 0.05$).

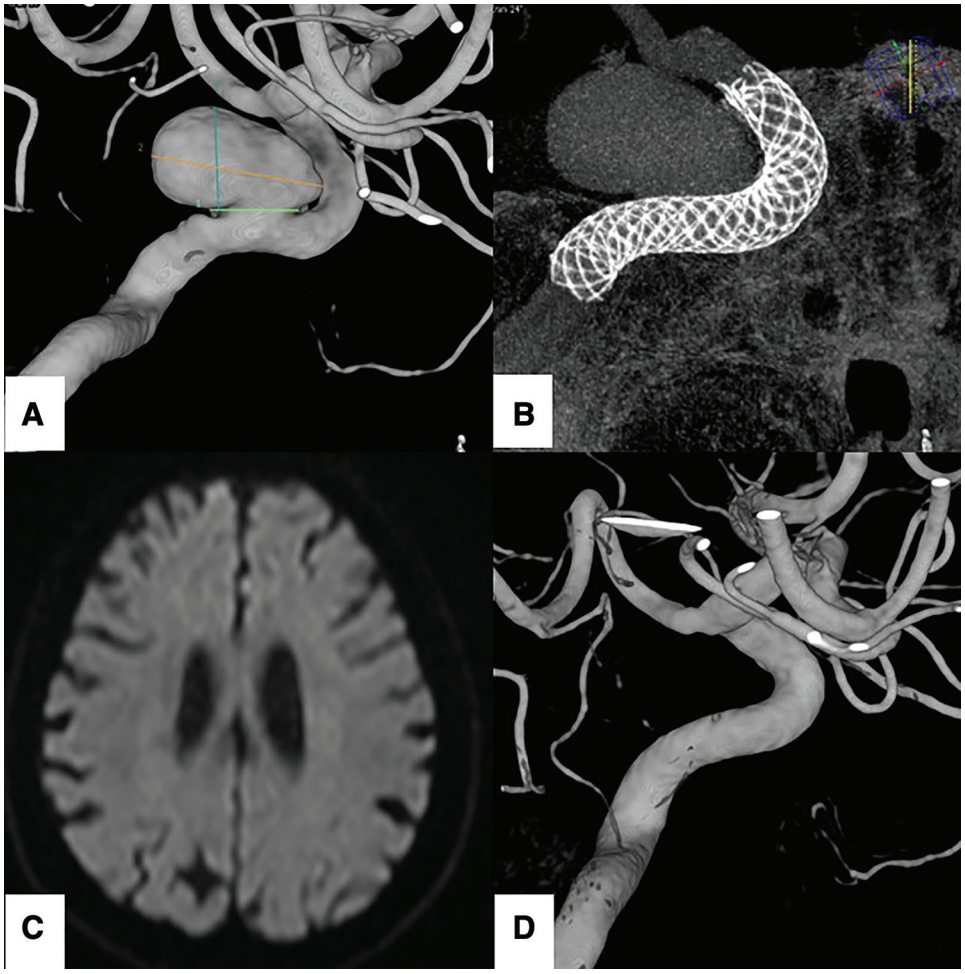

Fig. 3 Perioperative images and angiographical follow-up. (**A**) A Pipeline Flex 5.0 × 16.0 mm was placed for the unruptured aneurysm in the ICA C4 portion. (**B**) We confirmed good crimping of the stent by CBCT. (**C**) Postoperative MRI showed no hyper-intense area on DWI. (**D**) The aneurysm almost disappeared angiographically by 1 year after treatment. CBCT: cone beam computed tomography; DWI: diffusion-weighted imaging; ICA: internal carotid artery

The insufficient drug efficacy group consisted of one patient alone, but this patient had not received an EPA or statin preparation.

A representative case in which the dose of CLP was regulated based on the results of a platelet aggregation test is presented below.

Case: A 78-year-old woman

FD insertion for a right internal carotid artery aneurysm (maximum diameter: 15.8 mm, neck: 8.1 mm) was performed (**Fig. 3**). The oral administration of ASA at 81 mg and CLP at 75 mg was started 14 days before treatment. On preoperative assessment at the time of admission (2 days before treatment), the drug efficacy was evaluated as highly excessive (G type: –3, PATI: >8, aggregation rate at Ch 4: 5%). The dose of CLP was reduced to 50 mg. On reassessment on the 5th postoperative day (POD), the drug efficacy was evaluated as highly excessive (G type: –3, PATI: >8, aggregation rate at Ch 4: 17%), although the optimal range was almost reached. CLP at 50 mg was administered every 2 days, and follow-up assessment on the 13th POD revealed that the optimal range (G type: 0, PATI: 2.8, aggregation rate at Ch 4: 100%) had been reached (**Fig. 4**). During the subsequent 13-month follow-up, there was no ischemic or hemorrhagic complication.

Discussion

In all, 42 consecutive patients in whom DAPT (ASA + CLP) was introduced before EVT, platelet aggregation testing using an HTZ was possible. In 20 in whom CLP administration was continued after treatment, its dose was regulated

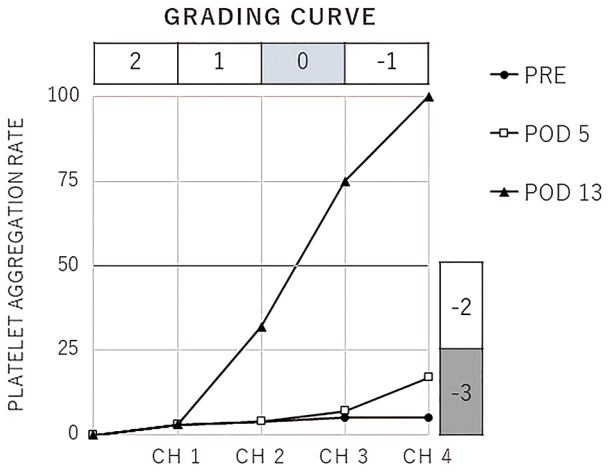

Fig. 4 Representative case of oral dose adjustment of CLP according to platelet aggregation activity. Preoperative evaluation revealed G type -3, PATI >8, 5% aggregation rate in Chanel 4 (black circle marker). Re-evaluation at POD5 with 50-mg CLP showed G type -3, PATI >8, and agglutination rate 17% in Channel 4 (white square marker). The result of re-evaluation following POD 13 with 50-mg CLP every other day was G type 0, PATI 2.8, and 100% aggregation rate in Channel 4 (black triangle marker). CLP: clopidogrel; PATI: platelet aggregatory threshold index; POD: postoperative day

based on the test results. On preoperative assessment, the drug efficacy was evaluated as excessive in many patients, but it was able to be adjusted to the optimal range by reducing the dose of CLP, as shown in **Figs. 1** and **2**. To date, there has been no hemorrhagic or embolic complication.

LTA is adopted as the platelet aggregation test in many cases. However, for this method, centrifugation is necessary to prepare platelet-rich plasma (PRP) and testing procedures are complex; 2–3 hours are required for testing, raising an issue. Furthermore, considering the influence of adipose components in blood on the results of this test, blood collection after fasting is recommended and a blood sample volume of approximately 10 mL is required.[13] The principle of the VerifyNow system is similar to that of LTA and this system facilitates simple testing through the use of a cartridge containing a platelet-aggregation-inducing agent (time required: ≤1 hour).[14] However, in Japan, testing using this system is not covered by health insurance and its running cost is high; it is inappropriate for regular monitoring.

With HTZ used in this study, platelet aggregation is evaluated using the SFP method. In this method, after a platelet-aggregation-inducing substance (ADP, collagen) is added to whole blood, aspiration through a micromesh filter (diameter: 30 μm) is performed to measure the aspiration pressure associated with blood-clot-related clogging. The PATI, as a minimum concentration of a platelet-aggregation-inducing substance required to obtain secondary aggregation, is calculated from an intersection point between a grading curve obtained by attaching four concentrations of the platelet-aggregation-inducing substance and 50% aggregation rate. Based on the PATI, the drug efficacy is evaluated in six grades (G type evaluation). This method is not influenced by blood adipose components, differing from LTA. Therefore, blood collection after fasting and centrifugation for preparing PRP are unnecessary. Testing can be conducted using approximately 2 mL of whole peripheral blood in a short time (**Table 2**).

The SFP method is highly correlated with LTA and is useful for evaluating the effects of antiplatelet drug administration.[11,12] However, no study has reported its use for the regulation of antiplatelet drugs before/after EVT. Regarding PATI-based evaluation using G type evaluation, the data were classified in comparison with those previously obtained using LTA, but its clinical significance has not been established. Therefore, in this study, in patients in whom the drug efficacy was evaluated as slightly excessive, the dose of CLP was not reduced at that point and dose reduction was reviewed only in patients in whom the drug efficacy became excessive during follow-up. At our hospital, drug adjustment is not determined based on the HTZ results alone, but by comprehensively evaluating the risks of embolism and hemorrhage in individual patients. Furthermore, no study has directly compared the PATI or aggregation rate obtained from HTZ with the P2Y12 reaction unit (PRU) value on the VerifyNow system. Therefore, in the future, it may be necessary to use different cutoff values of the PATI and aggregation rate when embolic complications are suspected in patients in whom the drug efficacy is evaluated as being within the optimal range using HTZ or when intraoperative thrombus formation is observed.

The most important advantage of HTZ is that measurement can be frequently conducted in each patient for the following reasons: its running cost is lower than that of the VerifyNow system and testing procedures are simpler than those for conventional LTA. In this study, 76 sessions of measurement were conducted in 20 patients (mean frequency: 3.8 times/patient) to evaluate platelet aggregation. Recently, a phenomenon of change in drug efficacy after the start of oral antiplatelet drug administration, known as delayed conversion, was reported. Delgado et al. assessed platelet aggregation using the VerifyNow system in 48 patients in whom an FD was inserted. In 77% in whom the PRU value was within its optimal range (80 <PRU <200) before treatment, the efficacy of CLP was evaluated as excessive 1 month after treatment. P2Y12 receptors were

Table 2 Comparison with other inspection methods

	Traditional methods	VerifyNow	HTZ
Measuring method	LTA	LTA	SFP
Sample	PRP	Whole blood	Whole blood
Requirement	10 mL	2 mL	1 mL
Timing of blood collection	Fasting state	Any time	Any time
Procedure	Complicated (required centrifugal separation)	Easy	A little complicated (reagent preparation)
The time required	2–3 hours	Within an hour	Within an hour
Reports	Many	Many	Few

HTZ: Hematracer ZEN (DS medical, Tokyo, Japan); LTA: light transmission aggregometry; PRP: platelet rich plasma; SFP: screen filtration pressure; VerifyNow (Accumetrics, San Diego, CA, USA)

excessively suppressed in 62% of all patients.[9] Furthermore, Nakagawa et al. adopted assessment using the VerifyNow system in 61 patients who underwent coil embolization of cerebral aneurysms, and noted preoperative hyperresponsiveness to CLP (PRU: <95) in 9 patients (15%), whereas it was observed in 25 (41%) patients 7 days after treatment, demonstrating a significant increase.[15] In this study, the drug efficacy also became excessive in 4 (33%) of 12 patients in whom the dose of CLP was not adjusted based on the results of preoperative assessment, requiring dose reduction. Concerning the timing when the drug efficacy was confirmed to be excessive, the interval from the start of oral administration was 21 and 14 days in 2 each, suggesting that only a single session of measurement immediately before treatment is insufficient. Furthermore, there was no patient with a reduction in the efficacy of CLP.

In this study, the drug efficacy was evaluated as insufficient in one patient (2.4%). According to previous studies using the VerifyNow system, hyporesponsiveness to CLP was noted in 9.8–36.5% of patients, being more frequent than in this study.[7,8,15] HTZ may not have detected patients with hyporesponsiveness to CLP on assessment using the VerifyNow system. However, in this study, there was no embolic complication related to antiplatelet drugs in any patient in whom CLP continuation or dose reduction was performed. In one patient in whom the drug efficacy was evaluated as insufficient, CLP was switched to prasugrel (oral preparation). In Japan, the indication of prasugrel is limited to combination therapy with ASA in percutaneous coronary intervention (PCI) patients in the cardiovascular field, but the percent dependence on CYP2C19, whose genetic polymorphism is frequent, is low and the number of patients with unresponsiveness is small. Many previous studies reported the safety and efficacy of prasugrel in EVT.[16,17]

As factors that influence the responsiveness to CLP on a platelet aggregation test using the VerifyNow system, combination therapy with EPA preparations, which may reduce the PRU value,[18] and statin preparations, which may increase the PRU value,[19,20] were reported. In this study, there were no significant differences in the rate of patients who received EPA or statin preparations between the excessive CLP efficacy and optimal groups on preoperative assessment. However, the number of patients was small.

The limitations of this study were as follows: the number of patients was small, measurement was not conducted during the non-administration period, and it is difficult to compare the results between the presence and absence of oral CLP administration. Furthermore, our method cannot be compared with other test methods, including the VerifyNow system. To our knowledge, no study has reported the use of HTZ for antiplatelet drug adjustment during the perioperative period before/after EVT. The clinical significance of the PATI and G type evaluation obtained from HTZ should be examined in the future. Since the start of HTZ use in our hospital, there has been no antiplatelet-drug-derived embolic or hemorrhagic complication, but assessment in more patients is necessary.

Conclusion

For EVT, the platelet aggregation test using HTZ is inexpensive/simple and can be repeatedly conducted. It may be useful for regulating antiplatelet drugs. On the other hand, no consensus regarding the interpretation of results or drug-regulating methods has been reached, requiring further assessment.

Disclosure Statement

The authors declare no conflicts of interest.

References

1) Fiorella D, Thiabolt L, Albuquerque FC, et al: Antiplatelet Therapy in Neuroendovascular Therapeutics. *Neurosurgery Clin N Am* 2005; 16: 517–540.
2) Hwang G, Jung C, Park SQ, et al: Thromboembolic complications of elective coil embolization of unruptured aneurysms: the effect of oral antiplatelet preparation on periprocedural thromboembolic complication. *Neurosurgery* 2010; 67: 743–748; discussion 748.
3) Fukushima-Uesaka H, Saito Y, Maekawa K, et al: Genetic variations and haplotypes of CYP2C19 in a Japanese population. *Drug Metab Pharmacokinet* 2005; 20: 300–307.
4) Hoshino K, Horiuchi H, Tada T, et al: Clopidogrel resistance in Japanese patients scheduled for percutaneous coronary intervention. *Circ J* 2009; 73: 336–342.
5) Jeong YH, Koh JS, Kang MK, et al: The impact of generic clopidogrel bisulfate on platelet inhibition in patients with coronary artery stents: results of the ACCEL-GENERIC study. *Korean J Intern Med* 2010; 25: 154–161.
6) Goh C, Churilov L, Mitchell P, et al: Clopidogrel hyperresponse and bleeding risk in neurointerventional procedures. *AJNR Am J Neuroradiol* 2013; 34: 721–726.
7) Fifi JT, Brockington C, Narang J, et al: Clopidogrel resistance is associated with thromboembolic complications in patients undergoing neurovascular stenting. *AJNR Am J Neuroradiol* 2013; 34: 716–720.
8) Delgado Almandoz JE, Kadkhodayan Y, Crandall BM, et al: Variability in initial response to standard clopidogrel therapy, delayed conversion to clopidogrel hyper-response, and associated thromboembolic and hemorrhagic complications in patients undergoing endovascular treatment of unruptured cerebral aneurysms. *J Neurointerv Surg* 2014; 6: 767–773.
9) Delgado Almandoz JE, Crandall BM, Scholz JM, et al: Last-recorded P2Y12 reaction units value is strongly associated with thromboembolic and hemorrhagic complications occurring up to 6 months after treatment in patients with cerebral aneurysms treated with the pipeline embolization device. *AJNR Am J Neuroradiol* 2014; 35: 128–135.
10) Oishi H, Teranishi K, Nonaka S, et al: Symptomatic very delayed parent artery occlusion after flow diversion stent embolization. *Neurol Med Chir (Tokyo)* 2016; 56: 350–353.
11) Tabuchi A, Taniguchi R, Takahashi K, et al: Action of aspirin on whole blood-aggregation evaluated by the screen filtration pressure method. *Circ J* 2008; 72: 420–426.
12) Mikami H, Terasawa F, Nakanishi K, et al: Utility of monitoring antiplatelet drug with a whole blood aggregation meter. *J Jpn Coll Angiol* 2005; 45: 1019–1025. (in Japanese)
13) Tomiyama Y, Satoh K, Ozaki Y, et al: Outline of "Recommendations for the standardization of light transmission aggregometry: a consensus of the working party from the platelet physiology subcommittee of SSC/ISTH". *Jpn J Thromb Hemost* 2016; 27: 365–369. (in Japanese)
14) Enomoto Y: Monitoring and optimizing antiplatelet therapy in patients with cerebrovascular disease. *Curr Pract Neurosurg* 2018; 28: 694–700. (in Japanese)
15) Nakagawa I, Yokoyama S, Park HS, et al: Possibility of active management of the target P2Y12 reaction unit range in patients undergoing aneurysmal neurointerventional procedures. *J Cereb Blood Flow Metab* 2017; 28: 241–247.
16) Podlasek A, Al Sultan AA, Assis Z, et al: Outcome of intracranial flow diversion according to the antiplatelet regimen used: a systematic review and meta-analysis. *J Neurointerv Surg* 2020; 12: 148–155.
17) Arimura K, Imamura H, Sakai C: Safety and efficacy of prasugrel with endovascular treatment for unruptured cerebral aneurysm. *JNET J Neuroendovasc Ther* 2017; 11: 553–557.
18) Hosogoe N, Ishikawa S, Yokoyama N, et al: Add-on antiplatelet effects of eicosapentaenoic acid with tailored dose setting in patients on dual antiplatelet therapy. *Int Heart J* 2017; 58: 481–485.
19) Suh JW, Cha MJ, Lee SP, et al: Relationship between statin type and responsiveness to clopidogrel in patients treated with percutaneous coronary intervention: a subgroup analysis of the CILON-T trial. *J Atheroscler Thromb* 2014; 21: 140–150.
20) Lau WC, Waskell LA, Watkins PB, et al: Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: a new drug-drug interaction. *Circulation* 2003; 107: 32–37.