Platelet Aggregability as a Predictor of Restenosis Following Carotid Endarterectomy

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Background: Antiplatelet drugs are administered before and after carotid endarterectomies (CEAs), but their efficacy for preventing restenosis remains unclear. Hence, this study aimed to identify associations between postoperative restenosis and platelet aggregability in CEA patients. *Methods:* Thirty-six consecutive CEA patients treated at Tokyo Women's Medical University from May 2013 to March 2015 were included in this retrospective study. Restenosis was defined as a stenosis ratio greater than or equal to 50% per the European Carotid Surgery Trial criteria or peak systolic velocity of 150 cm/s on carotid ultrasound. Platelet aggregability was measured turbidimetrically using a light-transmission platelet aggregometer and analyzed in terms of aggregation profiles for 2 concentrations of collagen used to induce aggregation (.25 and 2.0 μg/mL). Patients were automatically divided into 9 classes (Class 1-9, from the lowest to the highest aggregability) using a software program according to area under their platelet aggregation curves. Each class was subdivided into 10 further gradations for a total of 90 possible scores (10-99) using a software program. Patients were divided into high- and low-platelet aggregability score groups (cut-off = 49). *Results:* Data were analyzed for 36 of the 99 patients. Restenosis was observed in 10 (28%) patients. Restenosis incidence was significantly higher in patients with high-platelet aggregability score than in those with low-platelet aggregability score (50.0% [7/14] versus 13.6% [3 of 22]: $P = .0176$, odds ratio = 6.34, 95% CI: 1.27-31.57). *Conclusions:* Platelet aggregability is a useful metric for predicting and preventing restenosis after CEA. It has potential as an indicator for determining the optimal dose of antiplatelet drugs.

Key Words: Platelet aggregation—carotid endarterectomy—restenosis—light transmission aggregometer—Hema Tracer 313M—platelet function assay—antiplatelet therapy—NSR-II

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Introduction

Carotid endarterectomy (CEA) is a well-established procedure for preventing stroke in patients with carotid stenosis, regardless of symptoms. The North American Symptomatic Carotid Endarterectomy Trial[1] and the Asymptomatic Carotid Atherosclerosis Study[2] provided Class I evidence of the superiority of CEA against oral medication-based approaches for stroke prevention. Furthermore, CEA is associated with low morbidity and mortality, making it a safe intervention for patients with carotid stenosis. Many studies have investigated the incidence of restenosis after CEA and the estimates vary widely, ranging from .5% to 30%.[3-12] Many risk factors for restenosis have been proposed, including the use of statins, the presence of hypoechoic plaques on carotid

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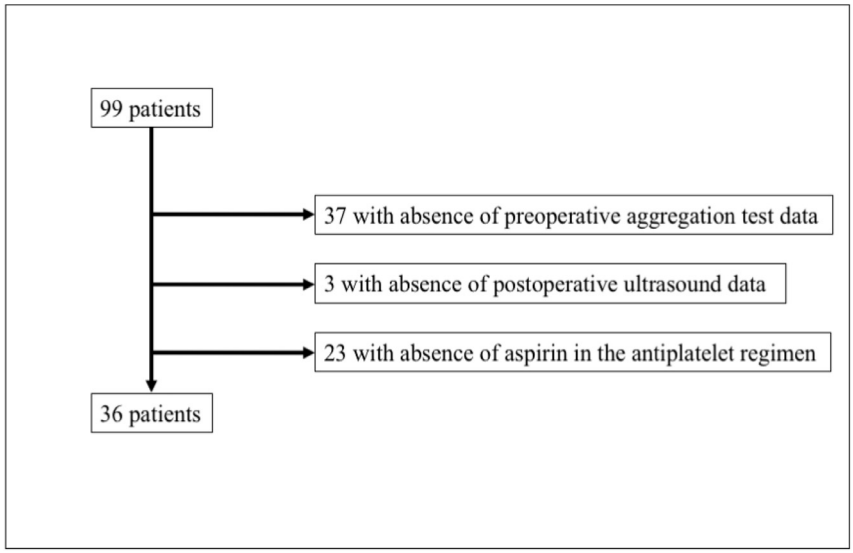

Figure 1. *Study criteria flowchart.*

ultrasound, diabetes, hypertension, female gender, smoking, the use of patch angioplasty during CEA, metabolic syndrome, and antiplatelet drugs.[3,6-8,11,13,14] However, no definitive preventative therapies for restenosis have been established.[6-8,11,15-17]

Antiplatelet drugs are somewhat protective against restenosis but their efficacy is still controversial.[3,4,6,9,12,18] One potential reason for this uncertainty is the difficulty of assessing and quantifying the efficacy of antiplatelet drugs. To this end, some recent reports have examined platelet aggregability as a useful metric for evaluating antiplatelet drug efficacy.[19-22]

This retrospective study of CEA patients aimed to identify associations between postoperative restenosis and platelet aggregability.

Subjects and Methods

The initial study population was composed of 99 consecutive patients with CEA treated at the Department of Neurosurgery of Tokyo Women's Medical University (Tokyo, Japan) between May 2013 and March 2015. Data were analyzed from 36 patients who underwent a platelet aggregation test before the procedure and who also underwent a postoperative carotid ultrasound examination. Sixty-three patients were excluded. The reasons for exclusion included the absence of: (1) preoperative aggregation test data ($n = 37$), (2) postoperative ultrasound data ($n = 3$), and (3) aspirin in the antiplatelet regimen ($n = 23$) (Fig 1). This study was approved by an institutional review committee (3640) and verbal informed consent was obtained from the participants.

Patient Backgrounds

Table 1 details the characteristics of the included patients. Patients were assigned to a high- or low-platelet aggregability score group based on the results of their platelet aggregation tests. These groups were statistically compared to check for associations between aggregability and restenosis.

Restenosis Evaluation

Restenosis was defined as a stenosis ratio greater than or equals to 50% per the European Carotid Surgery Trial criteria or peak systolic velocity of 150 cm/s on carotid ultrasound at both 6 and 12 months after CEA.

Surgical Procedure

The surgical indication for CEA in our institution was defined as over 60% stenosis per the European Carotid Surgery Trial criteria in asymptomatic patients or over

Table 1. *Patient characteristics*

Parameters	All patients ($n = 36$)
Age, mean ± SD	72.0 ± 8.0
Male:female, *n*	32:4
Medical history, *n* (%)	
Hyperlipidemia	25 (69.4)
Diabetes mellitus	11 (30.5)
Hypertension	26 (72.2)
Smoking	21 (58.3)
Medication	
ASA	27 (75.0)
ASA + CLO	8 (22.2)
ASA + CILO	1 (2.8)
Statin	26 (72.2)
Average stenosis ratio, mean ± SD	73.2 ± 12.0
Symptomatic: asymptomatic, *n*	15:21

Abbreviations: ASA, acetylsalicylic acid; CILO, cilostazol; CLO, clopidogrel.

50% stenosis in symptomatic patients. All CEAs were performed by the same surgeon using the same procedure. The common carotid artery was clamped using bulldog forceps and the internal carotid artery and the external common carotid artery were clipped. All patients had a shunt in place during carotid clamping. The plaque was removed along with the hypertrophic intima and the resection stump was closed with a tacking suture. The carotid artery was repaired using primary closure, rather than patch angioplasty. Resolution of stenosis was confirmed in all patients on postoperative carotid ultrasound before discharge.

Antiplatelet Drugs

All patients took oral antiplatelet drugs until the day of the surgery and resumed on postoperative day 3. The regimen consisted of either aspirin monotherapy (100 mg/d); dual antiplatelet therapy of aspirin and clopidogrel (75 mg/d); or aspirin and cilostazol (100/200 mg/d). We prescribed aspirin as the first choice. If patients were prescribed some antiplatelet drugs from the previous doctor, we continued the drugs as per the prescription.

Platelet Aggregability Measurement

Fasting venous blood was collected from an elbow vein without applying a tourniquet at an outpatient visit or after admission the day before the operation. Platelet aggregability was measured using a light-transmission platelet aggregometer (Hema Tracer 313M, LMS Corp., Tokyo, Japan) with a software program, the Natural Standard Range II (NSR-II; LMS Corp., Tokyo, Japan), which was specific to the equipment. Two concentrations of collagen were used to induce aggregation (low = .25 μg/mL; high = 2.0 μg/mL), which was specified by the NSR-II. Platelet aggregability was evaluated in terms of the maximum aggregation ratio and area under the curve at both concentrations (Fig 2). Patients were automatically grouped into 1 of 9 classes based on the results of the NSR-II (ie, Class 1-9, from lowest to highest aggregation; Fig 3). At Tokyo Women's Medical University, these classes were automatically subdivided into 10 further gradations with an add-on modification to the NSR-II software (NSR-II-M; LMS Corp., Tokyo, Japan), resulting in 90 possible aggregation scores (ie, 10-99; Fig 4). Patients rated greater than or equals to 49 were analyzed as the "high-platelet aggregability score" group (HAS), while those rated less than or equals to 48 were analyzed as the "low-platelet aggregability score" group (LAS). This cut-off point was obtained from the Receiver operating characteristic (ROC) curve.

Statistics

Continuous variables are presented as mean ± SD. Statistical testing was performed using JMP Pro 12.1.0 (SAS Institute Inc., Cary, NC). Data were analyzed using the chi-squared test or Fisher's exact test. Statistical significance was set at $P < .05$ for all tests.

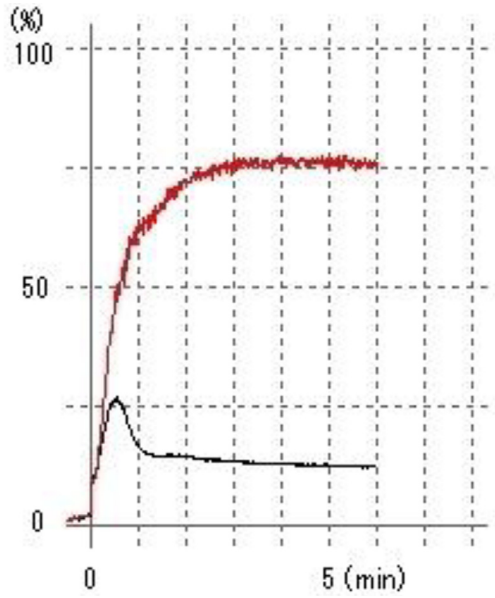

Figure 2. *Representative platelet aggregation curve.*
The upper and lower curves correspond to data obtained using the high- and low-concentration reagents (collagen; 2.0 and .25 μg/mL, respectively). The y-axis indicates the aggregation ratio, with higher values corresponding to higher platelet aggregability.

Results

Table 2 shows a breakdown of restenosis incidence by antiplatelet regimen. Of the 36 patients, 27 were on aspirin monotherapy, while 9 were on dual antiplatelet therapy with aspirin (aspirin + clopidogrel, $n = 8$; aspirin + cilostazol, $n = 1$).

Platelet Aggregability

The mean platelet aggregability score was 39.5 ± 17.6. There were 22 HAS patients (61.1%) and 14 LAS patients (38.9%). Table 3 shows patient characteristics separately for the HAS and LAS groups. No variables were significantly different between the two groups.

Restenosis Rates and Risk Factors

Restenosis was observed in 28% (10/36) of patients. Restenosis incidence was significantly higher in the HAS group than in the LAS group (50.0% [7/14] versus 13.6% [3/22]: $P = .0176$) (Table 4). Patients with restenosis were statistically similar to patients without events in terms of statin medications, hypertension, hyperlipidemia, diabetes, smoking history, antiplatelet regimen, mean stenosis rate, and symptomatic cases.

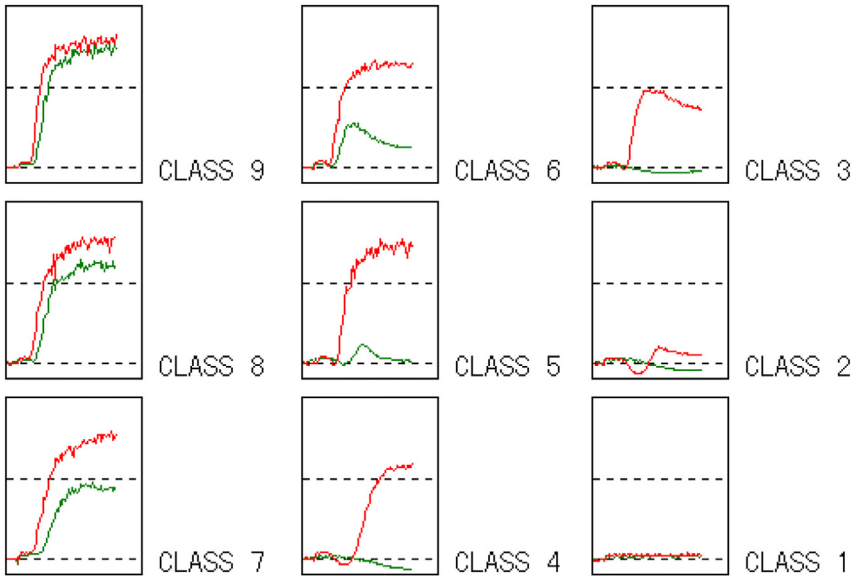

Figure 3. *Platelet aggregability by class (NSR-II).*

The upper and lower curves correspond to data obtained using the high- and low-concentration reagents (collagen; 2.0 and .25 μg/mL, respectively). The x-axis indicates time and the y-axis indicates the aggregation ratio. The graphs demonstrate that the higher the class number, the higher the platelet aggregability. Aggregation is first visible in the high-concentration reagent curve and then in the low-concentration reagent curve.

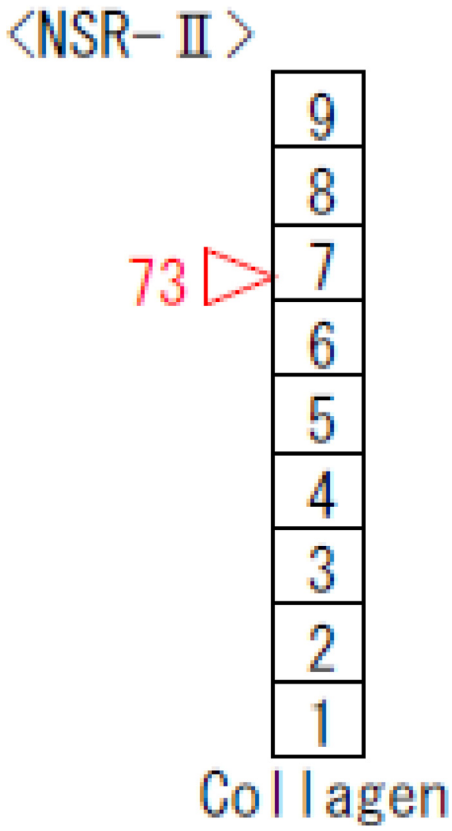

Figure 4. *The aggregability subclassification scheme used at Tokyo Women's Medical University.*

Classes 1-9 (Fig 3) were subdivided into 10 further gradations with a modified software (modified NSR-II), resulting in 90 possible aggregation scores (ie, 10-99). This figure indicates that platelet aggregability increases as scores increase from 11 to 99.

Discussion

Previous studies have investigated the incidence of restenosis after CEA and the estimates vary widely, ranging from .5% to 30%. The restenosis rate in our study (28%) was within the range past reported; however, it was higher than that of the CREST trial (6.3%).[23] This might be due to the difference between our definition of restenosis (50%) and the definition of restenosis in the CREST trial (70%).

Antiplatelet drugs are generally prescribed after CEA to prevent ischemic complications, but their protective effects against restenosis are controversial.[3,4,6,9,12,18] At least one report has concluded that they effectively prevent restenosis after CEA[12] but several studies have concluded otherwise.[4,9,24]

Previous reports failed to find significant associations between antiplatelet drugs and restenosis possibly because they did not monitor how well the drugs suppressed platelet aggregability. The efficacy of antiplatelet drugs can vary greatly from person to person and some patients are nonresponders.[19,20] Thus, the inconsistent results obtained in studies to date could be attributed to their failure to adequately evaluate the efficacy of antiplatelet drugs by monitoring platelet aggregability before surgical intervention.

Currently, there are a variety of testing equipments and assessment methods for measuring platelet aggregability with no clearly established standard. In this study, we evaluated platelet aggregability using a turbidimetric aggregometer using the NSR-II software, which measures aggregation in response to two concentrations of an inducing agent. We utilized a unique add-on modification, the

Table 2. *Breakdown of antiplatelet therapy*

	Total ($n = 36$)	Restenosis (+) ($n = 10$)	Restenosis (−) ($n = 26$)
ASA, *n* (%)	27 (75.0)	8 (80.0)	19 (73.1)
ASA + CLO, *n* (%)	8 (22.2)	2 (20.0)	6 (23.1)
ASA + CILO, *n* (%)	1 (2.8)	0 (0)	1 (3.8)

Abbreviations: ASA, acetylsalicylic acid; CILO, cilostazol; CLO, clopidogrel.

NSR-II-M, which captures finer gradations of aggregability. Platelet aggregability was classified into 9 groups by the NSR-II software and then further classified by the NSR-II-M. We used 49 as the cut-off point taking the ROC curve and our data distribution into consideration; however, more number of patients were needed to decide an accurate cut-off value.

Patients classified as having HAS using our innovative system experienced restenosis at a significantly higher rate than those classified as having LAS. This finding suggests that low-platelet aggregability may have a protective effect against restenosis in patients after CEA.

Studies have identified many risk factors for restenosis, including the use of statins, the presence of hypoechoic plaques on carotid ultrasound, diabetes, hypertension, female gender, smoking, the use of patch angioplasty during CEA, metabolic syndrome, and use of antiplatelet drugs.[3,6-8,11,13,14] However, these studies failed to establish a clear risk factor for restenosis, since the significant factors are inconsistent among the reports.[15] Our data showed no significant differences between patients with restenosis and patients without events in terms of other factors apart from platelet aggregability, ie, female sex, age, statin usage, hypertension, hyperlipidemia, diabetes, smoking history, antiplatelet regimen, mean stenosis rate, and symptomatic cases. Our monitoring-based aggregability score was the only variable that was statistically significant.

Intimal hyperplasia is critically involved in the development of restenosis 1 to 2 years after surgery.[9,25,26] Several studies have identified associations between antiplatelet drug efficacy and intimal hyperplasia.[18,24,27] In fact, antiplatelet drugs have been shown to suppress intimal hyperplasia in animal studies[26-28] and in experimental vein grafts.[28] Intimal hyperplasia develops as a result of the chemotactic migration of smooth muscle cells to the tunica intima after injury and their subsequent proliferation.[18,26] This migration is believed to be promoted by platelet aggregation and platelet-derived growth factors.[18,24,27,29-31] The suppression of platelet aggregability using antiplatelet drugs seems like a promising approach for inhibiting intimal hyperplasia and preventing restenosis.

Limitations

Only 36 of the 99 patients in the initial study population were included. We excluded patients who were not taking aspirin because of our use of collagen as the aggregation-inducing agent. However, this greatly increased the number of excluded cases. In addition, this was a retrospective observational study; thus, a prospective investigation, with a uniform antiplatelet regimen, is necessary to confirm our findings. Moreover, we did not search for correlations between high-platelet aggregability and antiplatelet dose. Dose increments are recommended for

Table 3. *Aggregation class background*

	Total number of patients ($n = 36$)	Suppression of aggregability (−) ($n = 14$)	Suppression of aggregability (+) ($n = 22$)	*P* value
Age, mean ± SD	72.0 ± 8.0	70.1 ± 8.5	73.2 ± 7.3	.305
Male:female, *n*	32:4	12:2	19:3	.99
Medical history, *n* (%)				
Hyperlipidemia	25 (69.4)	10 (71.4)	15 (68.2)	.99
Diabetes mellitus	11 (30.5)	5 (35.7)	6 (27.3)	.716
Hypertension	21 (58.3)	9 (64.3)	17 (77.3)	.462
Smoking	25 (69.4)	8 (57.1)	13 (59.1)	.908
Medication, *n* (%)				
ASA	27 (75.0)	12 (85.7)	15 (68.2)	.432
ASA + CLO	8 (22.2)	2 (14.3)	6 (27.3)	.441
ASA + CILO	1 (2.8)	0 (0)	1 (4.5)	.99
Statin	26 (72.2)	11 (78.6)	15 (68.2)	.706
Average stenosis ratio, mean ± SD	73.2 ± 12.0	72.1 ± 11.4	73.8 ± 12.3	.69
Symptomatic:asymptomatic, *n*	15:21	5:9	10:12	.732

Abbreviations: ASA, acetylsalicylic acid; CILO, cilostazol; CLO, clopidogrel.

Table 4. *Univariate analysis of risks factors for restenosis*

	Restenosis (−) ($n = 26$)	Restenosis (+) ($n = 10$)	*P* value	Odds ratio
Suppression of aggregability score (±), *n* (%)	19 (73.1)	3 (30.0)	.018*	6.34
Suppression of aggregability score (−), *n* (%)	7 (26.9)	7 (70.0)		
Age, mean ± SD	71.1 ± 7.4	73.2 ± 8.8	.492	
Medical history, *n* (%)				
Hyperlipidemia	19 (73.1)	6 (60.0)	.454	
Diabetes mellitus	8 (30.8)	3 (30.0)	.99	
Hypertension	19 (73.1)	7 (70.0)	.99	
Smoking	15 (57.7)	6 (60.0)	.99	
Medication, *n* (%)				
ASA	19 (73.1)	8 (80.0)	.99	
ASA + CLO	6 (23.1)	2 (20.0)	.99	
ASA + CILO	1 (3.8)	0 (0)	.99	
Statin	19 (73.1)	7 (70.0)	.99	
Average stenosis ratio, mean ± SD	74.6 ± 11.9	69.4 ± 11.2	.27	
Symptomatic:asymptomatic, *n*	11:15	4:6	.99	

Abbreviations: ASA, acetylsalicylic acid; CILO, cilostazol; CLO, clopidogrel.
*Statistically significant ($P < .05$).

patients who are nonresponsive to antiplatelet drugs after percutaneous coronary intervention.[32] However, one study found that dosages did not correspond to significant differences in ischemic event incidence rates after percutaneous coronary intervention.[33] Thus, it is uncertain whether increasing the dosage of an antiplatelet regimen can effectively prevent restenosis in nonresponsive patients.

Conclusions

Using antiplatelet drugs to lower the platelet aggregability score may effectively protect against restenosis after CEA. Our results suggest that monitoring the cut-off value of platelet aggregability using the score could also be applied to determine the optimal dosage of antiplatelet drugs, as an additional way to mitigate restenosis risk.

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