Association between Postprocedural Infarction and Antiplatelet Drug Resistance after Coiling for Unruptured Intracranial Aneurysms

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ABSTRACT

BACKGROUND AND PURPOSE: Procedure-related thromboembolism is a major limitation of coil embolization, but the relationship between thromboembolic infarction and antiplatelet resistance is poorly understood. The purpose of this study was to verify the association between immediate postprocedural thromboembolic infarction and antiplatelet drug resistance after endovascular coil embolization for unruptured intracranial aneurysm.

MATERIALS AND METHODS: This study included 338 aneurysms between October 2012 and March 2015. All patients underwent postprocedural MR imaging within 48 hours after endovascular coil embolization. Antiplatelet drug resistance was checked a day before the procedure by using the VerifyNow system. Abnormal antiplatelet response was defined as >550 aspirin response units and >240 P2Y12 receptor reaction units. In addition, we explored the optimal cutoff values of aspirin response units and P2Y12 receptor reaction units. The primary outcome was radiologic infarction based on postprocedural MR imaging.

RESULTS: Among 338 unruptured intracranial aneurysms, 134 (39.6%) showed diffusion-positive lesions on postprocedural MR imaging, and 32 (9.5%) and 105 (31.1%) had abnormal aspirin response unit and P2Y12 receptor reaction unit values, respectively. Radiologic infarction was associated with advanced age (65 years and older, \( P = .024 \)) only with defined abnormal antiplatelet response (aspirin response units >550, P2Y12 receptor reaction units >240). P2Y12 receptor reaction unit values in the top 10th percentile (>294) were associated with radiologic infarction (\( P = .003 \)). With this cutoff value, age (adjusted odds ratio, 2.29; 95% confidence interval, 1.28–4.08), P2Y12 receptor reaction units (>294; OR, 3.43; 95% CI, 1.53–7.71), and hyperlipidemia (OR, 2.05; 95% CI, 1.04–4.02) were associated with radiologic infarction in multivariate analysis.

CONCLUSIONS: Radiologic infarction after coiling for unruptured aneurysm was closely associated with age. Only very high P2Y12 receptor reaction unit values (>294) predicted postprocedural infarction. Further controlled studies are needed to determine the precise cutoff values, which could provide information regarding the optimal antiplatelet regimen for aneurysm coiling.

ABBREVIATIONS: ARU = aspirin response unit; DPL = diffusion-positive lesion; PRU = P2Y12 receptor reaction unit

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MATERIALS AND METHODS
This retrospective study included patients from a database prospectively collected between October 2012 and March 2015. This study was approved by the institutional review board, and informed consent was waived. During the given period, 470 unruptured aneurysms were treated in a single tertiary hospital. Among these, 129 cases were excluded due to lack of postprocedural MR imaging. There were no symptomatic infarctions among the excluded patients. Three cases with procedural rupture were also excluded, leaving 309 patients with 338 unruptured intracranial aneurysms for inclusion in this study.

Patient information, including sex, age, diabetes mellitus, hypertension, hyperlipidemia, smoking history, aneurysm profile including the size and location of the aneurysm, medical history, and pre- and postprocedural neurologic symptoms, was obtained from retrospective chart review. We also reviewed the number of angiograms obtained per intervention and total procedural time, which was considered to total anesthesia time.

Aneurysm size was categorized according to the long diameter on 3D digital subtraction angiography as small (<7 mm) and large (≥7 mm). Aneurysm location was categorized into internal carotid artery, anterior cerebral artery, middle cerebral artery, and posterior circulation systems. Postprocedural MR imaging was performed between 24 and 48 hours after the embolization procedure, and included diffusion-weighted imaging and time-of-flight (with 3D volume-rendered imaging). MRIs were reviewed by 2 independent board-certified radiologists. If hyperintense diffusion-positive lesions (DPLs) were detected on DWI, the remission of the thrombus was confirmed with subsequent angiography. A bolus of intravenous heparin (60 IU/kg) was injected at the time of catheter insertion, and activated clotting times were assessed hourly. If the activated clotting time after heparinization was shorter than 2–3 times from the baseline, an additional 1000 IU of heparin was injected to maintain an acceptable activated clotting time throughout the procedure. In cases with stent-assisted coil embolization, heparinization was maintained until 24 hours postprocedure on the basis of activated partial thromboplastin time tests performed every 4 hours. In addition, although we mostly used the single-catheter technique, we recorded the use of multiple catheters because using an additional catheter was reported to increase the risk of thromboembolic complications during the procedure.

Antiplatelet Therapy and Antiplatelet Function Test
Preprocedural antiplatelet therapy included aspirin (100 mg) and clopidogrel (75 mg) daily for 7 days before the elective endovascular coil embolization, regardless of stent usage. Response to the antiplatelet agents was evaluated in all patients the day before the procedure by using the VerifyNow P2Y12 assay (Accumetrics, San Diego, California). Because there was no definite evidence of association between antiplatelet drug resistance and immediate thromboembolic complications after coil embolization, the antiplatelet regimen was altered according to stent usage and the attending physician’s discretion. An abnormal antiplatelet response was defined as >550 aspirin response units (ARUs) and/or >240 P2Y12 receptor reaction units (PRUs). Also, we tried to investigate and clarify the optimal cutoff values of both ARUs and PRUs that were associated with DPL, which have been controversial in the literature.

Coil Embolization Procedures
Endovascular coil embolization was performed with the patient under general anesthesia. All procedures were performed by 2 neurointerventional experts at our center by using a biplane angiographic unit (Artis zee; Siemens, Erlangen, Germany). During the procedure, all patients were injected intravenously with heparin to prevent thromboembolic infarction. If thrombus was caused by using a catheter or wire during the procedure, the thrombus was immediately dissolved by using intravenous glycoprotein IIb/IIIa receptor inhibitor (tirofiban, Aggrastat), and the remission of the thrombus was confirmed with subsequent angiography. A bolus of intravenous heparin (60 IU/kg) was injected at the time of catheter insertion, and activated clotting times were assessed hourly. If the activated clotting time after heparinization was shorter than 2–3 times from the baseline, an additional 1000 IU of heparin was injected to maintain an acceptable activated clotting time throughout the procedure. In cases with stent-assisted coil embolization, heparinization was maintained until 24 hours postprocedure on the basis of activated partial thromboplastin time tests performed every 4 hours. In addition, although we mostly used the single-catheter technique, we recorded the use of multiple catheters because using an additional catheter was reported to increase the risk of thromboembolic complications during the procedure.

RESULTS
Baseline characteristics of patients are detailed in Table 1. Among 338 unruptured intracranial aneurysms, 263 (77.8%) were small (<7 mm) and 75 (22.2%) were large (≥7 mm). Stent-assisted embolization was performed in 148 (43.8%) cases, and a multiple microcatheter technique was performed in 118 (34.9%) cases. Antiplatelet function tests showed 32 (9.5%) ARU abnormalities and 105 (31.1%) PRU abnormalities. Complete embolization was achieved in 290 (85.8%) cases based on postprocedural MR imaging. Mean total procedural time was 168 ± 49 minutes. Because lack of precise value of total procedure time, this value was excluded in multivariate analysis. The univariate analysis showed that total procedural time was significantly associated with DPL (DPL versus no DPL, 193 ± 61 minutes versus 166 ± 48 minutes; P = .04).
Aneurysm (≥7 mm) lesions, and 13 cases (9.7%) had large (small-dot (<15 mm) lesions. One hundred twenty-one cases (90.3%) were 16 had contralateral lesions, and 29 had both ipsilateral and con- tralateral lesions. One hundred twenty-one cases (90.3%) were

Any Diffusion-Positive Lesion

Univariate analyses showed that advanced age (65 years or older) (P = .006), incomplete occlusion (P = .016), and dome size of the aneurysm (≥7 mm) (P = .016) were associated with the presence of a DPL (P < .05). However, ARU (P = .448) and PRU (P = .337) abnormalities were not associated with DPL in this data-

Multiple Diffusion-Positive Lesions (n ≥ 6)

Advanced age (65 years or older) (P = .017), incomplete occlusion (P = .033), and large aneurysm size (≥7 mm) (P = .012) were associated with multiple DPLs. ARU (P = .215) and PRU (P = .399) abnormalities were not associated with multiple (≥6) DPLs. Multivariate analysis showed that advanced age (65 years or older) (P = .030; OR, 2.47; 95% CI, 1.09–5.39), incomplete occlusion (P = .039; OR, 2.66; 95% CI, 1.05–6.76), and thrombus formation (P = .010; OR, 9.93; 95% CI, 1.86–97.10) were associated with multiple DPLs (P < .05).

Optimal Cutoff Value of Antiplatelet Resistance

DPLs were not associated with ARUs by scatterplot (Fig 3). The number of in-

DISCUSSION

Recent studies have demonstrated that high-on-treatment platelet reactivity was associated with symptomatic infarction and an increased the risk of mortality.11,21,22 However, pa-

Several studies support the idea that clopidogrel resistance can increase postprocedural thromboembolic complications, and our preliminary study showed similar results.4,11,12,22 Hwang et al10 recently reported that abnormal PRUs were associated with symptomatic infarction and that modified antiplatelet preparation could reduce the rate of thromboembolic events in coil em-


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postprocedural thromboembolic infarction was not closely associated with antiplatelet hyporesponders. This disparity is likely the result of different definitions of abnormal antiplatelet response and different outcome measurements because the PRU cutoff value varied widely among studies.4,10,11 Our results showed that abnormal PRUs (>240) were not associated with DPL, but PRU values in the upper 10th percentile (>294) were associated with DPL. These different results suggest that only nonresponse is associated with a higher thromboembolic risk.

Different outcome-measurement approaches could be another source of the contradictory results. Hwang et al10 used symptomatic infarction and procedural thrombus formation as the primary outcome. In this study, the primary outcome was the presence of a diffusion-positive lesion rather than symptomatic infarction because there were only 2 cases of symptomatic infarction in this case series. Instead, multiple (>6) small-dot lesions were categorized, and the association with variables was studied because multiple (>6) small-dot lesions on immediate postprocedural MR imaging were closely associated with symptomatic infarction in a previous study.7 We hypothesized that image-guided analysis would be more objective and that the possibility of missing a thromboembolic event would be lower. If a patient had a silent infarction, his or her death could be confused with that of a patient without complications.

A previous study showed that advanced age (65 years or older) was the only predictor of diffusion lesions after coil embolization. The authors suggested that tortuous vascular structures and underlying atherosclerotic burden could cause these results.8 Our findings support the findings of this previous study. Almekhlafi et al12 reported that during carotid artery stent placement, microemboli could occur during stent deployment or advancement through the stenosis. Thromboembolic complications could occur by dislodging thrombi from atherosclerotic vessels proximal to the target site and cracking the atherosclerotic plaque.12 Therefore, the use of wires or a catheter at the target site would cause thromboembolic...


events by dislodging thrombi from the atherosclerotic vessels at the aortic arch level. In this situation, nonipsilateral DPL occurred after the procedure. However, there are no data regarding the degree of atherosclerosis and tortuosity of the aortic arch.

For further evaluation and to identify the source of thromboembolism during coiling, CT angiography including the aortic arch could be helpful. Softer and smaller caliber catheters and wires and more skillful techniques could reduce the chance of dislodging thrombi during the procedure. Hwang et al. reported that incomplete occlusion is a risk factor for delayed ischemic stroke due to induced blood flow disturbance or stagnation. This study suggests that incomplete occlusion could be a source of infarction in both immediate and delayed thromboembolism. In addition, incomplete occlusion and large aneurysm size could explain frequent thromboembolism due to struggling to achieve complete occlusion of an aneurysm. These attempts could prolong the duration of procedure. Therefore, increased procedural time could possibly lead to thromboembolic complications in the postprocedural period. Mani and Eisenberg reported that the thromboembolic complication rate increases when the arteriographic procedure exceeds 80 minutes. Our study also showed that procedural time was associated with postprocedural DPL.

The 5 patients experiencing thrombus formation during the procedure had variable aneurysm diameters, neck sizes, and antiplatelet resistance. Among these patients, 4 had asymptomatic DPLs on postprocedural MR imaging and 1 showed no DPL or symptoms. Although thrombus formation during the procedure showed a statistically significant difference on multiple DPLs in multivariate logistic analyses, the procedure did not show a similar tendency.

Table 2: Patient clinical, laboratory, and procedural variables associated with any DPL and multiple DPLs (≥6) on univariate and multivariate logistic analyses

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tivariate logistic regression analysis, thrombus formation during embolization of unruptured aneurysm seems to be benign with the appropriate usage of a glycoprotein IIb/IIIa inhibitor.

Limitations
Several limitations of this study should be noted. First, although this study uses prospectively collected data, patient data were obtained from retrospective chart review. Therefore, minimal, transient symptoms could be missed in this analysis. Second, this study did not include the effect of systemic heparinization during the procedure. Despite maintaining heparinization during the procedure, precise activated clotting time control was difficult due to various patient responses to injected heparin. Third, the primary outcome of this study was DPL rather than symptomatic infarction. Although we hypothesized that image-based analysis could be more objective, these data may not have clinical significance. Fourth, these data were analyzed at an aneurysm level due to classification difficulties. Difficulties occurred when an individual patient had multiple aneurysms. Analyzing the patient at an aneurysm level prevents such difficulties because the individual aneurysms are checked into the database separately. Additionally, we analyzed the data at a patient level and found that there were no significant differences in the patient-level clustering data results.

Last, some experts recommended analyzing the clinical association with procedural time, the number of angiograms performed per intervention, and DPL. The exact time of each procedure was not included in our registry database. According to our retrospective chart review, we could only obtain anesthesia time, not procedural time. The univariate analysis revealed that anesthesia time was solely associated with DPL but not the number of angiograms performed per intervention. However, anesthesia time could differ from procedure time due to other procedure time associated with anesthesia. Therefore, we did not include total procedural time in multivariate analysis. In addition, we did not include the number of angiograms obtained per intervention in multivariate analysis because they were associated with DPL in univariate analysis. Procedural time could be a potential predictor of DPL because it relates to the difficulty of coil embolization. These variables could be potential predictors of postprocedural DPL and could be considered important variables in further study.

CONCLUSIONS
Postprocedural DPL was closely associated with advanced age. Only clopidogrel nonresponse (PRU >294) could predict DPL after unruptured aneurysm coiling. The antiplatelet regimen should be individualized on the basis of the receiver operating characteristics. Further studies are needed to determine precise cutoff values, which may provide a rationale for the optimal antiplatelet regimen for aneurysm coiling.

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