Original Investigation | CLINICAL TRIAL

Standard vs Modified Antiplatelet Preparation for Preventing Thromboembolic Events in Patients With High On-Treatment Platelet Reactivity Undergoing Coil Embolization for an Unruptured Intracranial Aneurysm
A Randomized Clinical Trial

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IMPORTANCE Thromboembolism is the most common complication in coiling for an unruptured aneurysm and is frequent in patients with high on-treatment platelet reactivity (HTPR) who are prescribed a standard antiplatelet preparation for its prevention.

OBJECTIVE To evaluate the effect of a modified antiplatelet preparation compared with a standard preparation in patients with HTPR undergoing coiling.

DESIGN, SETTING, AND PARTICIPANTS A prospective randomized open-label active-control trial with blinded outcome assessment at the Seoul National University Bundang Hospital from May 27, 2013, to April 7, 2014. Patients with HTPR were randomly assigned (1 to 1) to the standard or modified preparation group. Patients without HTPR were assigned to the non-HTPR group. A total of 228 patients undergoing coiling for unruptured aneurysms were enrolled and allocated to the study, 126 in the HTPR group (63 to the standard preparation group and 63 to the modified preparation group) and 102 to the non-HTPR group. Intent-to-treat analysis was performed.

INTERVENTIONS The modified preparation (HTPR to aspirin, 300 mg of aspirin and 75 mg of clopidogrel bisulfate; and HTPR to clopidogrel, 200 mg of cilostazol added to the standard regimen) was performed before coiling in the modified preparation group. Standard preparation (100 mg of aspirin and 75 mg of clopidogrel) was maintained in the standard preparation and non-HTPR groups.

MAIN OUTCOMES AND MEASURES The primary outcome was a thromboembolic event defined as thromboembolism during coiling and a transient ischemic attack or ischemic stroke within 7 days after coiling. The principal secondary outcome was a bleeding complication according to Thrombolysis in Myocardial Infarction bleeding criteria within 30 days after coil embolization.

RESULTS The thromboembolic event rate was low in the modified preparation group (1 of 63 [1.6%]) compared with the standard preparation group (7 of 63 [11.1%]; adjusted risk difference, −11.7% [95% CI, −21.3% to −2.0%]; $P = .02$), which had a higher thromboembolic risk than the non-HTPR group (1 of 102 [1.0%]; adjusted risk difference, 8.6% [95% CI, 1.0% to 16.3%]; $P = .03$). All bleeding complications were of minimal grade according to Thrombolysis in Myocardial Infarction bleeding criteria. The bleeding rate was not different between the modified (6 of 63 [9.5%]) and standard (4 of 63 [6.3%]) preparation groups (adjusted risk difference, 5.6% [95% CI, −4.2% to 15.4%]; $P = .26$).

CONCLUSIONS AND RELEVANCE Modified antiplatelet preparation for patients with HTPR compared with standard antiplatelet preparation reduced the thromboembolic event rate in coiling for an unruptured aneurysm without increasing bleeding.

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Coil embolization as an effective treatment to prevent bleeding from an intracranial aneurysm is being increasingly performed for unruptured intracranial aneurysms. The development of coil embolization devices and techniques has reduced procedural complications but thromboembolic events, which are an inherent problem of endovascular treatment, still remain the most frequent complications, leading to serious neurological deficit in patients undergoing coil embolization for an unruptured intracranial aneurysm.[1]

Antiplatelet medication before coiling has been proposed to prevent a thromboembolic event[2] and an antiplatelet preparation (100 mg of aspirin and 75 mg of clopidogrel bisulfate daily) is being accepted as a standard preparatory step in coil embolization for an unruptured aneurysm because its effect and safety have been demonstrated.[3-6] However, a significant portion of patients undergoing neurointervention develop high on-treatment platelet reactivity (HTPR) during standard antiplatelet preparation and several studies have reported a 7% to 40% incidence of thromboembolic events during the periprocedural period in patients with HTPR.[4,7-10] To our knowledge, no strategies are currently available for patients with HTPR in whom coil embolization is considered for unruptured aneurysms.

We evaluated the effect and safety of a modified antiplatelet preparation to prevent thromboembolic events in patients with HTPR undergoing coil embolization for an unruptured intracranial aneurysm compared with patients using a standard antiplatelet preparation.

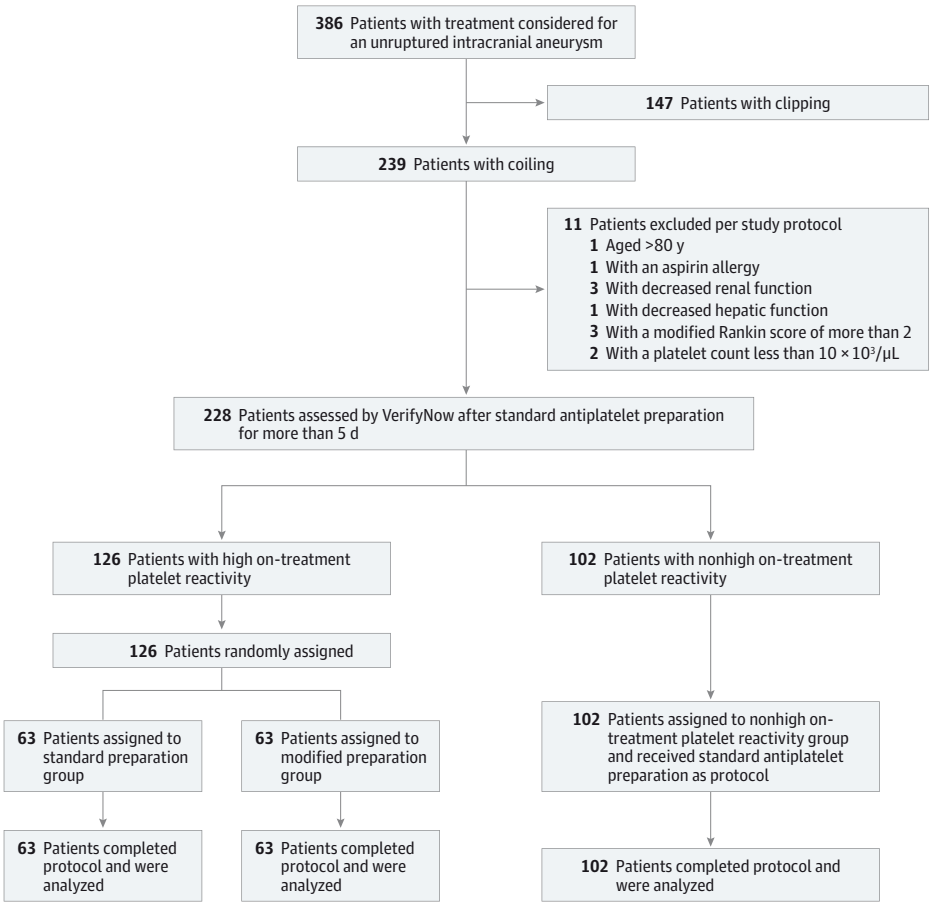
Methods

Study Design and Patients

This study was a prospective randomized open-label active-control trial with a blinded outcome assessment that took place at the Seoul National University Bundang Hospital from May 27, 2013, to April 7, 2014. The CONSORT flow diagram is shown in **Figure 1**. The institutional review board at the Seoul National University Bundang Hospital approved this study protocol, which can be found in the trial protocol in Supplement 1. All patients provided written informed consent.

Treatment was considered for patients with an unruptured aneurysm according to the guidelines of the Korean Stroke Society (eAppendix 1 in Supplement 2). The choice of clipping vs coiling was made by considering the risk of each method in a weekly conference with all vascular neurosurgeons and interventionists. We enrolled all consecutive patients who

Figure 1. CONSORT Flow Diagram



High on-treatment platelet reactivity was defined as 550 or more aspirin reaction units or more than 213 P2Y12 reaction units after administering the standard antiplatelet preparation (100 mg of aspirin and 75 mg of clopidogrel daily) for more than 5 days. To convert platelet count to $\times 10^9$/L, multiply by 1.

planned to undergo coil embolization. Participant eligibility for the study was confirmed with inclusion and exclusion criteria (eAppendix 2 in Supplement 2).

Study Procedures

A daily standard antiplatelet preparation regimen (100 mg of aspirin and 75 mg of clopidogrel) was prescribed for more than 5 days. We used an antiplatelet preparation in all study participants because antiplatelet preparation was shown to reduce the thromboembolic event rate without increasing bleeding complications, even in standard coiling without stent assistance.[3,11,12] Furthermore, we considered unexpected technical difficulties during the procedure, which would change simple coiling to stent-assisted coiling.

The patients were admitted 1 day before coil embolization and blood sampling was performed for the platelet function test. Platelet function was measured with the VerifyNow Aspirin Test and VerifyNow P2Y12 Test (Accumetrics). High on-treatment platelet reactivity was defined as 550 or more aspirin reaction units or more than 213 P2Y12 reaction units. Several parameters and cutoff values are applicable for defining HTPR to clopidogrel. In this study, we used more than 213 P2Y12 reaction units because P2Y12 reaction units better predicted the thromboembolic complications in patients undergoing coil embolization compared with percentage inhibition[4] and this cutoff value was found to be well correlated with flow cytometry, one of the criterion standard platelet response tests.[13,14] Based on results of the platelet function test, patients with HTPR were randomly assigned to the standard or modified preparation groups in a 1 to 1 ratio by a computer-generated randomization sequence.[15] Patients without HTPR were assigned to the non-HTPR group.

On the day of coil embolization, the standard antiplatelet regimen was maintained for patients in the standard preparation and non-HTPR groups. The modified antiplatelet regimen was administered to patients in the modified preparation group at least 4 hours before coiling. High-dose aspirin (300 mg) and clopidogrel (75 mg) were prescribed for patients with HTPR to aspirin. A loading dose of cilostazol (200 mg) was added to the standard antiplatelet regimen for patients with HTPR to clopidogrel. Because high-dose clopidogrel failed to reduce the thromboembolic event rate related with neurointervention in a previous cohort study,[8] we added cilostazol to the standard regimen for the modified antiplatelet preparation. Cilostazol, a phosphodiesterase 3 inhibitor, exhibits antiplatelet effects via inhibition of the conversion of cyclic adenosine monophosphate to 5′-adenosine monophosphate, causing a subsequent increase in cyclic adenosine monophosphate within platelets and has been shown to augment platelet inhibition when added to aspirin and clopidogrel.[16,17]

All aneurysm coil embolization procedures were conventional and described in the eAppendix 3 in Supplement 2. The standard or modified antiplatelet regimen was maintained after coiling in patients treated with stent-assisted coiling but was discontinued in patients treated with standard coiling without a stent, including single or multiple microcatheter techniques and balloon-assisted coiling if they had no disease requiring continuous antiplatelet therapy. Patients were monitored for 24 hours after the procedure and discharged the next day. Patients visited our outpatient clinic on days 7 and 30 after coiling if they did not experience any discomfort or complications. We instructed patients to visit the emergency department in our hospital regardless of a scheduled appointment after medical care at a primary or secondary care center near their home when any problem related to coil embolization occurred, even if it was transient. The outcomes and complications detected in the outpatient clinic or emergency department and all information reported by the patients were collected.

Outcomes

The primary outcome was a thromboembolic event during the early periprocedural period (within 7 days after coil embolization). A thromboembolic event was defined as a thromboembolism detected during the coiling procedure or a transient ischemic attack or ischemic stroke with evidence of infarction on diffusion-weighted imaging, which occurred in a vascular territory consistent with the location of the treated aneurysm.[3,4,11,12,18,19]

Secondary outcomes were bleeding complications according to Thrombolysis in Myocardial Infarction bleeding criteria within 30 days after coil embolization[20] and a thromboembolic event that occurred during the periprocedural period (within 30 days after coil embolization).[21]

Procedural imaging and clinical monitoring data of the study participants, including only participant numbers for identification, were electronically stored. The independent data and safety committee blinded to treatment assignments and patient information accessed these data at their remote sites using the Sync program (BitTorrent Inc).[22] The committee included Kyeong Sun Song, MD, Department of Neurosurgery, New Korea Hospital, Kimpo; Young Jin Lee, MD, Department of Neurosurgery, Pohang Stroke and Spine Hospital, Pohang, Korea; Arham Abrar, MD, Department of Neurosurgery, Dr Cipto Mangunkusumo National Hospital, Jakarta, Indonesia; and Nur Setiawan Suroto, MD, Department of Neurosurgery, Dr Sutomo General Hospital, Surayaba, Indonesia. They adjudicated all primary and secondary outcomes.

Statistical Analysis

In estimating the power for determining efficacy, we assumed that the effect of the modified antiplatelet preparation for reducing thromboembolic events would be similar to the difference in thromboembolic event rates between patients with and without HTPR. Therefore, the calculated study size was 114 patients with HTPR (57 in each group), assuming a thromboembolic event rate of 15% and 1% in the standard and modified preparation groups, respectively, within 7 days after coiling (rate difference, 14%). The anticipated event rates were based on results of a cohort study.[8] This sample size provided 80% power to detect this rate difference in the primary outcome at the 2-sided significance level of .05. Considering a dropout rate of 10%, we enrolled the study candidates, targeting 126 patients with HTPR (63 in each group).

The Wilcoxon rank sum test was used for continuous variables and the χ^2 or Fisher exact tests were used for nominal

Table 1. Baseline Characteristics of 228 Study Patients[a]

Variable	63 Patients With HTPR Standard Preparation, No. (%)	63 Patients With HTPR Modified Preparation, No. (%)	102 Patients With Non-HTPR, No. (%)
Antiplatelet resistance			
Aspirin	3 (4.8)	5 (7.9)	0
Clopidogrel	59 (93.6)	53 (84.2)	0
Both	1 (1.6)	5 (7.9)	0
None	0	0	102 (100)
Platelet function test reaction unit, mean (SD)			
Aspirin	428 (46.0)	448 (65.3)	403 (38.0)
P2Y12	251 (44.6)	250 (46.5)	146 (46.4)
Female	51 (81.0)	57 (90.5)	61 (61.8)
Age, mean (SD), y	59.6 (8.68)	59.7 (9.21)	54.1 (11.99)
Weight, mean (SD), kg	62.0 (10.32)	60.8 (9.98)	62.7 (10.6)
Body mass index, mean (SD)[b]	24.6 (2.86)	24.8 (3.55)	24.0 (3.02)
Smoking	6 (9.5)	2 (3.2)	12 (11.8)
Medical history			
Hypertension	34 (56.1)	29 (46.0)	38 (37.3)
Diabetes mellitus	12 (19.1)	12 (19.1)	14 (13.7)
Hyperlipidemia	16 (25.4)	12 (19.1)	24 (23.5)
Cerebrovascular accident	1 (1.6)	4 (6.4)	6 (5.9)
Coronary heart disease	5 (7.9)	1 (1.6)	1 (1.0)
Medication			
Statin	17 (27.0)	10 (15.9)	21 (20.6)
Proton pump inhibitor	2 (3.2)	1 (1.6)	4 (3.9)
Calcium channel blocker	22 (34.9)	19 (30.2)	16 (15.7)
NSAIDs	9 (14.3)	7 (11.1)	5 (4.9)
Laboratory data, mean (SD)			
White blood cell count, /μL	6581 (1649.4)	5913 (1447.8)	6623 (1988.7)
Red blood cell count, $\times 10^6$/μL	4.2 (0.42)	4.2 (0.46)	4.4 (0.40)
Hemoglobin level, g/dL	13.1 (1.24)	12.9 (1.43)	13.6 (1.36)
Hematocrit, %	38.6(3.28)	38.0 (3.81)	39.9 (3.52)
Platelet count, $\times 10^3$/μL	243 (55.5)	222 (56.0)	250 (55.2)
aPTT, s	36.7 (9.07)	36.3 (4.29)	35.7 (3.56)
PT INR, %	1.00 (0.062)	1.00 (0.065)	0.99 (0.053)
Total cholesterol level, mg/dL	182 (36.2)	187 (37.0)	181 (39.3)
Triglyceride level, mg/dL	133 (93.8)	116 (56.9)	141 (106.3)
HDL-C level, mg/dL	47 (14.2)	49 (10.2)	46 (10.5)
LDL-C level, mg/dL	106 (32.5)	107 (33.6)	103 (33.9)

(continued)

factors in comparisons of baseline characteristics. To explore whether patients with HTPR had a high risk of thromboembolic events with the standard preparation, the primary outcome of the standard preparation group was first compared with that of the non-HTPR group. Next, we performed principal analyses, comparisons of primary and secondary outcomes between the modified and standard preparation groups to evaluate the effect and safety of the modified antiplatelet preparation. All comparisons were performed by logistic regression analysis, adjusted for factors with clinical relevance among variables showing a baseline group difference at a *P* value of less than .20 and were provided with an adjusted risk difference (RD) and 95% CI.[23] Predefined subgroup analyses were performed to explore the uniformity of the overall primary outcome differences. The primary outcome was compared in the subgroups by aneurysm diameter and coiling method. The test for heterogeneity was performed with Q-statistics.[24] Statistical analyses were conducted using Stata statistical software, version 13 (StataCorp LP). Statistical significance was accepted for *P* values less than .05.

Results

A total of 386 patients underwent treatment for unruptured aneurysms between May 27, 2013, and April 7, 2014, and 239

Table 1. Baseline Characteristics of 228 Study Patients[a] (continued)

Variable	63 Patients With HTPR Standard Preparation, No. (%)	63 Patients With HTPR Modified Preparation, No. (%)	102 Patients With Non-HTPR, No. (%)
Aneurysm data			
Maximum size, mean (SD), mm	6.5 (3.03)	5.8 (2.18)	5.6 (2.16)
<7	43 (68.3)	49 (77.8)	81 (79.4)
≥7	20 (31.7)	14 (22.2)	21 (20.6)
Neck size, mean (SD), mm	4.5 (3.92)	3.7 (1.75)	4.0 (1.76)
≤4	34 (54.0)	47 (74.6)	69 (67.7)
>4	29 (46.0)	16 (25.4)	33 (32.3)
Dome-to-neck ratio, mean (SD)	1.1 (0.42)	1.2 (0.44)	1.1 (0.42)
≤1	28 (44.4)	26 (41.3)	54 (52.9)
>1	35 (55.6)	37 (58.7)	48 (47.1)
Location			
Anterior cerebral artery	11 (17.5)	6 (9.5)	19 (18.6)
Internal carotid artery	41 (65.1)	45 (71.4)	66 (64.7)
Middle cerebral artery	3 (4.8)	7 (11.1)	4 (3.9)
Posterior circulation	8 (12.7)	5 (7.9)	13 (12.8)
Atherosclerotic lesions in cerebral circulation	6 (9.5)	9 (14.3)	12 (11.8)
Procedural data			
Coiling			
Standard	20 (31.8)	22 (34.9)	27 (26.5)
Stent assisted	43 (68.2)	41 (65.1)	75 (73.5)
Occlusion grade[c]			
Complete	22 (34.9)	25 (39.7)	42 (40.2)
Residual neck	21 (33.3)	21 (33.3)	32 (32.4)
Residual sac	20 (31.7)	17 (27.0)	28 (27.4)
Packing density, mean (SD), %[d]	28.0 (7.84)	29.5 (9.04)	29.5 (8.68)
Procedure time, mean (SD), min	34.4 (13.12)	38.1 (18.46)	34.4 (17.68)

Abbreviations: aPTT, activated partial thromboplastin time; HDL-C, high-density lipoprotein cholesterol; HTPR, high on-treatment platelet reactivity; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; NSAIDs, nonsteroidal anti-inflammatory drugs; PT, prothrombin time.

SI conversion factors: To convert white blood cell count to $\times 10^9$/L, multiply by 0.001; to convert red blood cell count to $\times 10^{12}$/L, multiply by 1.0; to convert hemoglobin levels to grams per liter, multiply by 10.0; to convert hematocrit to a proportion of 1.0, multiply by 0.01; to convert platelet count to $\times 10^9$/L, multiply by 1.0; to convert aPTT to seconds, multiply by 1.0; to convert cholesterol levels to millimoles per liter, multiply by 0.0259; and to convert triglyceride levels to millimoles per liter, multiply by 0.0113.

[a] Group comparison was performed between the standard and modified preparation groups and between the standard preparation and nonhigh on-treatment platelet reactivity groups.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Evaluated according to the Raymond grade.

[d] Aneurysm volume was measured with the Integris, version 3.2 three-dimensional RA volume measuring tool (Philips Medical Systems) and coil volume was calculated online (http://www.angiocalc.com). Using these 2 volumes, packing density (%, coil/aneurysm volume × 100) was obtained.

consecutive patients were treated by elective coil embolization (Figure 1). Eleven patients were excluded and 228 patients were enrolled in this study. Of them, 126 (55.3%) had HTPR and were randomly assigned to the standard and modified preparation groups. The remaining 102 patients (44.7%) without HTPR were assigned to the non-HTPR group as study protocol.

Baseline clinical characteristics of the 228 patients are summarized in **Table 1**. Baseline characteristics of the standard and modified preparation groups were well balanced except for white blood cell (P = .01) and platelet (P = .02) counts as well as aneurysm neck size (P = .008). However, the group differences of white blood cell and platelet counts were not found to be clinically significant. In the standard preparation group, elderly (P = .01) and female (P = .001) patients were significantly more frequent than in the non-HTPR group. These demographic characteristics led to other differences in medical history (hypertension, P = .04; and coronary heart disease, P = .03), concomitant medication use (calcium channel blocker, P = .007; and nonsteroidal anti-inflammatory drugs, P = .05), and laboratory findings (red blood cell count, P = .005; hemoglobin level, P = .02; and hematocrit, P = .02).

Coil embolization was successful in all 228 patients. Thromboembolic events developed in 9 patients (3.9%) (**Table 2**) and were detected during coiling or within 7 days after coiling. One patient (case 4) had an additional thromboembolic event 14 days after coiling. Of the 9 patients with thromboembolic events, mild neurological deficit was shown in 4 patients at the 30-day follow-up and severe disability remained in 2 patients (cases 1 and 4) in the standard preparation group. Oozing from the femoral puncture site or a local groin hematoma categorized as minimal by the Thrombolysis

Table 2. Summary of Patients With Thromboembolic Events

Variable	Standard Preparation Group, Case No.							Modified Preparation Group, Case 8	Nonhigh On-Treatment Platelet Reactivity Group, Case 9
	1	2	3	4	5	6	7		
Age, y	61	60	70	70	57	63	63	70	58
Sex	Female	Female	Female	Female	Female	Female	Female	Female	Male
Aspirin reaction units, No.	478	403	398	466	411	394	491	412	377
P2Y12 reaction units, No.	297	222	269	254	327	220	221	230	125
Aneurysm type	Anterior communicating artery, 4.8 mm	Posterior communicating artery, 5.9 mm	Paraclinoid ICA, 6.6 mm	Ophthalmic artery, 9.1 mm	Paraclinoid ICA, 5.9 mm	Basilar bifurcation, 7.3 mm	Anterior choroidal artery, 2.5 mm	M1, 3.5 mm	Ophthalmic artery, 6.4 mm
Coiling method	Double microcatheter	Double microcatheter	Stent assisted	Stent assisted	Stent assisted	Stent assisted	Stent assisted	Stent assisted	Stent assisted
Thromboembolic event	Mental deterioration 30 min after coiling, thrombotic occlusion of parent artery	Right arm weakness 4 h after coiling, embolic event without parent artery occlusion	In-stent thrombosis during coiling	Aphasia and right hemiplegia 1 h after coiling and recurrent aphasia and right hemiparesis 14 d after coiling, thrombotic occlusion of the parent artery	Dysarthria and right hemiparesis 5 d after coiling, embolic event	In-stent thrombosis during coiling	Left facial palsy and arm weakness 6 d after coiling, embolic event	Motor aphasia and right hemiparesis 6 h after coiling, in-stent thrombosis	Right arm weakness 3 d after coiling, embolic event
Treatment	Intra-arterial fibrinolytics tirofiban infusion stent deployment	Conservative	Intra-arterial tirofiban infusion	Intra-arterial tirofiban infusion	Conservative	Intra-arterial tirofiban infusion	Conservative	Intra-arterial tirofiban	Conservative
Infarction area	Bilateral 1 ACA territories	Left thalamic	No infarction	Left MCA territory infarction	Left MCA embolic infarction	No infarction	Right anterior choroidal artery territory infarction	No infarction	Left MCA territory infarction
Modified Rankin Scale score[a]	5	1	0	4	1	0	1	0	1

Abbreviations: ACA, anterior cerebral artery; MCA, middle cerebral artery.

[a] Clinical outcome was evaluated 30 d after coiling using the modified Rankin Scale score.

Table 3. Primary and Secondary Outcomes of the Standard and Modified Preparation Groups

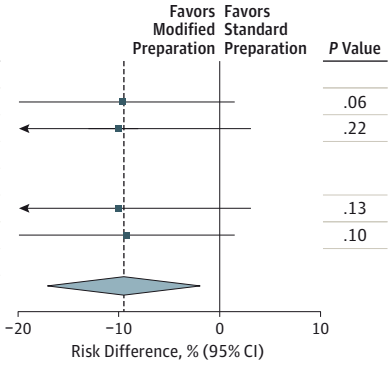
Variable	Modified Preparation, No. (%)	Standard Preparation, No. (%)	Crude Risk Difference, % (95% CI)	Adjusted Risk Difference, % (95% CI)[a]	*P* Value
Thromboembolic event, d					
≤7	1/63 (1.6)	7/63 (11.1)	−9.5 (−17.9 to −1.2)	−11.7 (−21.3 to −2.0)	.02
≤30[b]	1/63 (1.6)	7/63 (11.1)	−9.5 (−17.9 to −1.2)	−11.7 (−21.3 to −2.0)	.02
Bleeding event	6/63 (9.5)	4/63 (6.3)	3.2 (−6.2 to −12.6)	5.6 (−4.2 to −15.4)	.26

[a] Adjusted for age, statin use, and aneurysm neck size.

[b] A thromboembolic event recurred in a patient of the standard preparation group who had a thromboembolic event immediately after coiling.

Figure 2. Subgroup Analysis of the Primary Outcomes

Group	No./Total No. (%) With Thromboembolic Event: Modified Preparation	Standard Preparation	Risk Difference, % (95% CI)	*P* Value
Aneurysm Diameter				
≤7 mm	1/49 (2.0)	5/43 (11.6)	−9.6 (−20 to 0.8)	.06
>7 mm	0/14 (0)	2/20 (10)	−10.0 (−23.1 to 3.1)	.22
Heterogeneity: *P* = .97				
Coiling Method				
Standard	0/22 (0)	2/20 (10)	−10.0 (−23.1 to 3.1)	.13
Stent assisted	1/41 (2.4)	5/43 (11.6)	−9.2 (−19.9 to 1.5)	.10
Heterogeneity: *P* = .93				
Overall	1/63 (1.6)	7/63 (11.1)	−9.5 (−17.9 to −1.2)	



in Myocardial Infarction bleeding criteria occurred in 22 patients (9.6%). No bleeding complication defined as more than the minimal Thrombolysis in Myocardial Infarction bleeding criteria category was detected during 30 days after coil embolization. Other procedural complications were detected in 3 patients (1.3%; femoral puncture site infection in 1 patient, cystitis owing to a Foley catheter insertion in 1 patient, and a distal coil migration during coiling, which was removed with a microsnare in 1 patient).

Thromboembolic events within 7 days after coiling occurred frequently in the standard preparation group (7 of 63 [11.1%]) compared with those in the non-HTPR group (1 of 102 [1.0%]; crude RD, 10.1% [95% CI, 2.1% to 18.1%]). This difference was also found to be significant even when it was adjusted for sex, age, history of coronary heart disease, aneurysm diameter, and aneurysm neck size (adjusted RD, 8.6% [95% CI, 1.0% to 16.3%]; *P* = .03).

Primary and Secondary Outcomes

The frequency of thromboembolic events within 7 days after coiling in the modified preparation group was significantly lower than that in the standard preparation group (1 of 63 [1.6%] vs 7 of 63 [11.1%]; crude RD, −9.5%; adjusted RD, −11.7% [95% CI, −21.3% to −2.0%]; *P* = .02; **Table 3**). The bleeding complication rate was not different between the modified and standard preparation groups (6 of 63 [9.5%] vs 4 of 63 [6.3%]; crude RD, 3.2%; adjusted RD, 5.6% [95% CI, −4.2% to 15.4%]; *P* = .26). An additional thromboembolic event occurred 14 days after coiling in 1 patient (case 4) who already had a primary outcome event; therefore, the thromboembolic event rate within 30 days after coiling was the same as the primary outcome rate (1 of 63 [1.6%] vs 7 of 63 [11.1%]; crude RD, −9.5%; adjusted RD, −11.7% [95% CI, −21.3% to −2.0%]; *P* = .02).

Subgroup Analyses

The predefined subgroup analyses did not show statistically significant differences in the strata. However, the trend that the modified preparation group had a lower thromboembolic event rate compared with the standard preparation group was maintained regardless of aneurysm diameter or coiling method (**Figure 2**).

Discussion

In patients with HTPR who had a high risk of a thromboembolic event in coil embolization for an unruptured intracranial aneurysm, modified antiplatelet preparation, including a high dose of aspirin or the addition of cilostazol, reduced thromboembolic events compared with the standard antiplatelet preparation. Bleeding complications were not found to be more frequent in the modified antiplatelet preparation compared with the standard preparation.

Coil embolization for an unruptured intracranial aneurysm is a preventative treatment for future bleeding and resultant neurological deficit. Overall complications have decreased but substantial complications still occur in coil embolization for an unruptured aneurysm.[25] Considering the purpose of coil embolization for an unruptured aneurysm, its complication rate should be very low. Among these complications, thromboembolic events need to be primarily controlled because they are most frequent.[1]

Antiplatelet preparation before coil embolization was introduced and showed an effect.[2-6] However, we found that HTPR was detected in a significant portion of patients undergoing coil embolization during administration of the standard antiplatelet preparation and was associated with a high risk for thromboembolic events, which was consistent with other studies.[4,7-10] Therefore, to further reduce the thromboembolic event rate in coil embolization for an unruptured aneurysm, we suggest the modified antiplatelet preparation for patients with HTPR, which was effective in this study. Because thromboembolism occurs more frequently when coiling a large aneurysm or using a stent, it can be regarded as important only in these situations. However, the results of our subgroup analyses indicated that the modified antiplatelet preparation for the patients with HTPR can be beneficial regardless of aneurysm diameter or coiling method.

To our knowledge, no antiplatelet guideline for the coil embolization of intracranial aneurysm has existed prior to the current study. Antiplatelet protocol can be varied across neurointervention centers. However, if antiplatelet preparation has been included in center protocols, we recommend a platelet function test and modifying antiplatelet preparation based on its results before coil embolization.

In a large prospective cardiology trial, high-dose clopidogrel for patients with HTPR to clopidogrel, which was defined as 230 or more P2Y12 reaction units, failed to reduce the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis.[26] One possible explanation for this failure may be that the cutoff value of 230 is high for adequate platelet inhibition. It is supported by a post hoc analysis of this trial.[27] Therefore, we used a lower cutoff value of 213 for defining HTPR to clopidogrel in this study. This platelet overinhibition could lead to more serious bleeding complications but we only encountered minimal bleedings (femoral puncture site oozing or a local groin hematoma) without any serious bleeding complications. Therefore, our findings suggest that the risk of more inhibiting platelet function using the modified antiplatelet preparation does not outweigh its benefit in patients undergoing coil embolization for an unruptured aneurysm.

In this study, most thromboembolic events developed during the early periprocedural period. However, we also found that additional events occurred during the late period, especially in patients treated with stent-assisted coiling in whom continuous antiplatelet therapy was needed. This finding indicates that maintaining modified antiplatelet therapy after coil embolization is recommended for patients with HTPR after a stent-assisted coiling procedure. However, unlike periprocedural thromboembolic events, delayed thromboembolism in stent-assisted coiling, which occurs after 1 month of procedure, is not associated with inadequate platelet inhibition. Therefore, future research is needed to determine the optimal duration of modified antiplatelet therapy in patients with HTPR after stent-assisted coiling.

This study had several limitations resulting from being a single-center open-label study. We chose a single-center study because important confounding factors, such as selecting adequate patients for coil embolization and the proper coiling technique for each case, should be controlled. In this investigator-initiated study, without support from pharmaceutical company, it was impossible to obtain a placebo for blinding that was certified by the Korean Ministry of Food and Drug Safety. Therefore, we conducted this study as an open-label study. We strictly limited cointerventions for all study participants. Furthermore, to prevent a biased outcome ascertainment and adjudication, an independent data and safety committee blinded to the patient information evaluated all outcomes using imaging studies or structured criteria. Finally, silent infarction or positive diffusion-weighing imaging lesions were not considered in this study because a routine magnetic resonance evaluation after coil embolization is not recommended and clinical significance of positive diffusion-weighing imaging lesions is not clear.[21] However, because there is currently no single criterion for evaluating thromboembolic events, positive diffusion-weighing imaging lesions can be considered as a secondary outcome in future trials.

Conclusions

We found that a modified antiplatelet preparation with a high dose of aspirin or the addition of cilostazol for patients with HTPR compared with the standard preparation reduced the rate of thromboembolic events in coil embolization for an unruptured intracranial aneurysm without increasing the rate of bleeding complications. Our results suggest that modifying antiplatelet preparation based on a platelet function test before coil embolization is a safe and effective strategy.

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