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This information is current as
of August 6, 2025.

AJNR Am J Neuroradiol 2010, 31 (7) 1206-1210

doi: <https://doi.org/10.3174/ajnr.A2051>

<http://www.ajnr.org/content/31/7/1206>

ORIGINAL RESEARCH

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Preinterventional Clopidogrel Response Variability for Coil Embolization of Intracranial Aneurysms: Clinical Implications

BACKGROUND AND PURPOSE: Thromboembolism is one of the most serious complications in coil embolization for intracranial aneurysms, and antiplatelet premedication may reduce this complication. However, interindividual variation exists in the efficacy of CPG. This study sought to elucidate the clinical implications of preinterventional CPG response variability in patients who undergo coil embolization for intracranial aneurysms.

MATERIALS AND METHODS: CPG premedication was given to 186 consecutive patients with 209 aneurysms who underwent elective coil embolization, and the response to the premedication was measured by a point-of-care antiplatelet function test (VerifyNow assay). Patients were stratified into 4 quartiles according to the test results, and their correlation with the occurrence of periprocedural complications was analyzed. The contribution of a variety of variables to the high PRU was also tested.

RESULTS: In this cohort, rates of thromboembolic events and all adverse events were 7.5% and 9.1%, respectively. The quartiles of the P2Y12 reaction unit of the ADP channel (PRU) showed a significant tendency toward thromboembolic events ($P = .013$) and all procedure-related adverse events ($P = .009$), while those of the BASE and percentage inhibition did not. Thromboembolic events occurred in 17.0% and procedure-related adverse events, in 21.3% of the patients in the fourth quartile. Female sex was the only significant factor related to the fourth quartile of PRU in the multiple logistic regression analysis ($P = .014$).

CONCLUSIONS: Procedure-related thromboembolic events occurred more frequently in patients in the upper quartile with higher PRU, especially in the fourth quartile. Further study including a large number of patients is expected to confirm this finding.

ABBREVIATIONS: ADP = adenosine diphosphate; ANOVA = analysis of variance; BASE = iso-thrombin receptor activating peptide channel; CPG = clopidogrel; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PRU = residual platelet reactivity; ROC = receiver-operating characteristic; SPSS = Statistical Package for the Social Sciences

Thromboembolism is one of the most serious complications in coil embolization for intracranial aneurysms,¹⁻⁵ and antiplatelet premedication may reduce this complication.^{6,7} CPG is a P2Y12 ADP receptor antagonist^{5,8} and, through a series of clinical trials, has become a standard regimen in patients at risk of ischemic stroke and myocardial infarction.⁹⁻¹¹ However, there is a concern over increased risk of bleeding with combination antiplatelet therapy including CPG.^{12,13} On the other hand, the efficacy of prophylactic CPG therapy is variable among patients, and resistance to the antiplatelet therapy is considered the major cause of the variable response.^{14,15} The influence of high pretreatment platelet reactivity on the outcome of patients with intracranial aneurysms treated with coil embolization is not yet well-established, to our knowledge. This study sought to elucidate the clinical implication of preinterventional CPG response variability in patients who undergo coil embolization for intracranial aneurysms.

Materials and Methods

Patient Population

Since March 2006, CPG has been administered to patients with unruptured intracranial aneurysms before coil embolization in our institution. Since October 2008, we have measured the platelet reactivity after CPG premedication with a point-of-care antiplatelet function test (VerifyNow; Accumetrics, San Diego, California). We reviewed 186 consecutive patients with 209 aneurysms (116 internal carotid artery aneurysms, 46 anterior cerebral artery aneurysms, 28 middle cerebral artery aneurysms, and 19 posterior circulation aneurysms) who underwent the platelet activity measurement and elective coil embolization in our prospectively collected data base for neurointerventional procedures.

The baseline clinical and laboratory characteristics of the patients are presented in Table 1. "Nonsmokers" were defined as those who never smoked, and "smokers" included current and past smokers who have ever smoked 10 cigarettes per day for at least 1 year. Typically, a 300-mg loading dose of CPG was given the day before the procedure, and an additional 75 mg of CPG was given on the morning of the procedure in most cases ($n = 165$, 89%). Some patients had been taking antiplatelet agents other than CPG ($n = 29$). For chronic users of CPG, only a maintenance dose (75 mg) was administered without loading ($n = 21$, 11%). Among chronic users, 11 patients had been taking aspirin as well. After the embolization procedure, an antiplatelet agent was administered orally for ≥ 1 week, depending on

Received November 19, 2009; accepted after revision January 13, 2010.

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DOI 10.3174/ajnr.A2051

Table 1: Patients' clinical and laboratory characteristics (n = 186)^a

Characteristic	
Sex, male/female	57:129 (1:2.3)
Age (yr)	58.3 ± 10.2
Body weight (Kg)	63.6 ± 10.7
Hypertension	94 (51%)
Diabetes mellitus	15 (8%)
Statin use	31 (17%)
Smoking	
Smoker	36 (19%)
Nonsmoker	150 (81%)
Alcohol intake	36 (19%)
Hematocrit level (%)	38.2 ± 4.3
Platelet count (×10 ³ /μL)	227 ± 60
Total cholesterol level (mg/dL)	181.1 ± 36.8
Triglyceride level (mg/dL)	150.3 ± 85.6
HDL cholesterol level (mg/dL)	51.1 ± 17.5
LDL cholesterol level (mg/dL)	109.0 ± 32.5
Mode of medication	
CPG loading (300 mg) only	136 (73%)
Previous other antiplatelet medication plus CPG loading	29 (16%)
Continued CPG medication without loading	21 (11%)

^a All the continuous variables are presented as mean ± SD.

the presence of underlying atherosclerotic stenosis or protruded coil loops at the end of the procedure, or the stent placement during coil embolization. For example, patients who had a stent placed during the procedure were prescribed CPG for 1 month and the use of aspirin was prescribed for an indefinite period.

Coil Embolization Procedures and Procedure-Related Complications

Endovascular coil embolization was performed by using a standardized protocol in a neuroangiography suite, as described previously.^{16,17} General anesthesia was induced during most sessions. Systemic anticoagulation with heparin was used from the beginning of the procedure. Heparin was usually administered as a 3000-IU bolus intravenously just after the introducer sheath was inserted, followed by the administration of 1000 IU/h. A simple coiling procedure (composed of a single microcatheter placement and coil deployment), a multiple-microcatheter technique,^{18,19} a balloon remodeling technique,²⁰ and stent-supported coil embolization²¹ were used at the discretion of the operator.

The procedure-related thromboembolism was defined as thrombus formation and/or a distal embolism observed during the procedure or clinically recognized ischemic deficits that occurred within 60 days of the procedure.^{5,7} The procedure-related aneurysm perforation included both the "leak" and "nonleak" types.²² The former was defined as a demonstration of extra-aneurysmal contrast material, and the latter was defined as device extrusion from an aneurysm without contrast leakage.

Blood Sample Acquisition and Platelet Activity Measurement

Whole blood was obtained before the coil embolization procedure by puncture of the antecubital vein. Blood was placed into 1.8-mL-draw plastic Vacuette tubes (Greiner, Monroe, North Carolina) containing 3.2% sodium citrate, following a 5-mL discard, as previously described.²³ Residual platelet reactivity on CPG therapy was measured by using the VerifyNow P2Y12 assay (Accumetrics), a turbidimetric-based optical detection system that measures platelet aggregation.^{23,24}

This system measures platelet aggregation as an increase in light transmittance and produces 3 values, including BASE, PRU, and percentage inhibition. BASE is a platelet reaction unit measured after stimulation with an isothrombin-receptor-activating peptide and serves as an estimate of baseline platelet reactivity. PRU is measured from the channel stimulated with 20 μmol of ADP, reflecting residual P2Y12 receptor activity. Therefore, a high PRU value indicates less effectiveness of CPG therapy. Percentage inhibition is a calculated value from a formula: percentage inhibition = (BASE – PRU) / BASE × 100. In this study, patients were stratified into 4 quartiles according to the test results, and their correlation with occurrence of periprocedural complications was analyzed. The contribution of a variety of clinical (sex, age, body weight, mode of CPG premedication, hypertension, diabetes, statin usage, smoking habit, alcohol intake) and laboratory variables (hematocrit, platelet count, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol) to the high residual platelet reactivity was also tested.

Statistical Analyses

An unpaired Student *t* test, 1-way ANOVA, Tukey-Kramer multiple comparison test, and the χ^2 test for trends were performed with by using GraphPad InStat (Version 3.05 for Windows 95/NT; GraphPad Software, San Diego, California). Quartile values and histograms were produced with the SPSS (Version 13.0 for Windows; SPSS, Chicago, Illinois). Logistic regression analysis was also performed with SPSS to find factors related to high PRU values. Variables with *P* values < .10 in the simple logistic regression analysis were chosen as the variables for multiple logistic regression analysis. The ability of the test to discriminate between patients with and without a procedure-related thromboembolic event was evaluated by ROC curve analysis by using SPSS. The optimal cutoff value was calculated by determining the PRU value providing the greatest sum of sensitivity and specificity. *P* values < .05 were considered significant in all analyses.

Results

For this study population (*n* = 186), procedure-related adverse events occurred in 9.1% (17/186). These comprised 14/186 (7.5%) thromboembolic events and 3/186 (1.6%) procedural aneurysmal perforations (1 leak type and 2 nonleak type perforations). No patient had thromboembolism and aneurysmal perforation simultaneously. Among the 14 thromboembolic events, there were 9 cases of thrombi formation observed during the interventional procedures, 3 cases of acute symptomatic ischemic lesions without angiographic abnormality (5–24 hours after the procedures), and 2 cases of delayed symptomatic thromboembolism (11–32 days after embolization). All the thrombi found during the procedures were treated with intra-arterial tirofiban infusion (*n* = 8) or extended heparinization (*n* = 1) and did not produce any neurologic symptoms. There was no procedure-related permanent morbidity or mortality.

The mean values of test results were the following: BASE of 361.7 ± 52.8, PRU of 276.9 ± 78.0, and percentage inhibition of 23.1 ± 20.1. All the histograms of test results (BASE, PRU, and percentage inhibition) showed bell-shaped distributions. When quartiles of each variable (BASE, PRU, and percentage inhibition) were tested in relation to procedure-related adverse events, only those of PRU were found to be significant (Table 2). Thromboembolic events increased from 4.3% in the first quartile and 2.2% in the second quartile to 6.5% in the

Table 2: Frequency of procedure-related adverse events according to PRU

Quartile (No.)	PRU	Thromboembolic Events	Procedure-Related Aneurysmal Perforations	All Procedure-Related Adverse Events
1st (47)	<240	2 (4.3%)	1 (2.1%)	3 (6.4%)
2nd (46)	240–284	1 (2.2%)	0 (0%)	1 (2.2%)
3rd (46)	285–332	3 (6.5%)	0 (0%)	3 (6.5%)
4th (47)	>332	8 (17.0%)	2 (4.3%)	10 (21.3%)
<i>P</i> value ^a		.013	.605	.009

^a χ^2 test for trends.

Table 3: Relations between patients' characteristics and PRU^a

Clinical and Laboratory Variables	<i>P</i>	PRU
Sex (male)	<.001	244 ± 68 vs 291 ± 78
Age (younger than 65 years)	.028	268 ± 80 vs 295 ± 72
Body weight (≥60 Kg)	.031	267 ± 78 vs 292 ± 76
CPG medication (≥7 days)	.003	230 ± 96 vs 283 ± 74
Combination antiplatelet medication (yes)	.175	263 ± 83 vs 281 ± 76
Hypertension (no)	.745	275 ± 78 vs 278 ± 78
Diabetes mellitus (yes)	.184	251 ± 99 vs 279 ± 76
Statin use (no)	.198	274 ± 78 vs 293 ± 77
Smoking status (current or past smoker)	.071	256 ± 73 vs 282 ± 79
Alcohol intake (yes)	.157	260 ± 76 vs 280 ± 78
Hematocrit level (≥38%)	.008	263 ± 73 vs 293 ± 81
Platelet count (<227 × 10 ³ /μL)	.562	274 ± 80 vs 280 ± 76
Total cholesterol level (<200 mg/dL)	.232	273 ± 80 vs 288 ± 71
HDL cholesterol level (≥40 mg/dL)	.225	275 ± 79 vs 292 ± 69
LDL cholesterol level (≥130 mg/dL)	.608	273 ± 75 vs 280 ± 78
Triglyceride level (<200 mg/dL)	.091	274 ± 77 vs 299 ± 72
Procedure-related thromboembolism (no)	.061	274 ± 78 vs 318 ± 54

^a A group of patients denoted within the parentheses showed decreased residual platelet activity.

third quartile and 17.0% in the fourth quartile ($P = .013$). Procedure-related aneurysmal perforation occurred in the first (2.1%) and the fourth quartiles (4.3%) and showed no significant tendency related to PRU value. When all the procedure-related adverse events were considered, the tendency was also significant ($P = .009$). The rate of procedure-related adverse events amounted to 21.3% among the patients with a PRU value of >332.

We also analyzed the relationship between clinical and laboratory characteristics and PRU, as listed in Table 3. PRU values were significantly lower in men ($P < .001$), younger patients ($P = .028$), those with higher body weight ($P = .031$), those taking CPG for ≥7 days ($P = .003$), and those with higher hematocrit levels ($P = .008$). When we considered the mode of CPG administration, the patients who had been taking CPG for ≥7 days demonstrated significantly lower values of PRU and percentage inhibition compared with those groups with CPG loading without previous medication (Table 4).

When we tested variables in relation to the higher PRU values of >332, which is the cutoff value of the fourth quartile, sex ($P = .001$), body weight ($P = .009$), and hematocrit level ($P = .049$) were found to be significant on simple logistic regression analysis (Table 5). With multiple logistic regression analysis, female sex was the only significant factor related to the higher PRU values of >332 ($P = .014$). The ROC curve analysis showed that PRU levels significantly discriminate between patients with and without the procedure-related thromboembolic events with an area under the curve of 0.675 (95% confidence interval, 0.526–0.825; $P = .043$). A PRU

value of 295 was identified as the optimal cutoff point to predict the events, with a sensitivity of 75% and a specificity of 57%.

Discussion

Adequate inhibition of the platelet activity, as well as anticoagulation, is a principal concern for neurointerventional procedures, including coil embolization of intracranial aneurysms to prevent procedure-related adverse events. The VerifyNow system is one of convenient tools for measurement of platelet activity in response to CPG medication, and good correlations with ADP-induced platelet aggregation determined by using light transmittance aggregometry and vasodilator-stimulated phosphoprotein phosphorylation assay have been demonstrated.^{25–28} Until now various cutoff values of different parameters have been tested.^{23,29,30} When CPG resistance was defined as percentage inhibition <40%, 43%–52% of patients were CPG-resistant in the previous studies.^{29,30} When we applied this criterion to our series of patients, the rate of CPG resistance amounted to 84% (157/186). However, the incidence of procedure-related thromboembolic events (7.5%) was less than one-tenth of this number. Thus, we tried to find another viable criterion, the PRU value, which was found to be clinically applicable when we divided our patients into quartiles.

Thromboembolic events significantly increased from the first (4.3%) and second (2.2%) quartiles to the third (6.5%) and fourth (17.0%) quartiles ($P = .013$), and the fourth quartile PRU cutoff value was 332. While percentage inhibition reflects the individual patient's responsiveness to CPG treatment, PRU gives information on the residual platelet reactivity following antiplatelet treatment. For example, when a patient who is CPG-resistant demonstrates a high percentage inhibition value on the VerifyNow P2Y12 assay, he or she may show high or low PRU values based on the remaining platelet reactivity. In our study, percentage inhibition failed to reveal meaningful correlation with the outcome variables of procedure-related thromboembolic events or procedure-related complications. On the contrary, PRU was found to have a significant impact on the outcome variable. Several studies in the field of cardiology demonstrated that high PRU values were associated with increased periprocedural myocardial infarction as well as mortality after percutaneous coronary intervention.^{24,31}

Regarding the mode of CPG administration, chronic use (≥7 days) provided benefit in reducing platelet reactivity (Table 4). In our series, the chronic users had some reasons for the CPG prescription, including histories of previous cerebral infarction or coronary artery disease with or without percutaneous coronary intervention performed; otherwise we did give

Table 4: CPG therapy monitoring results according to the mode of administration

Mode of Administration	BASE	PRU	Percentage Inhibition
CPG loading (300 mg) only, 136 (73%)	360.8 ± 51.8	285.2 ± 71.6	20.6 ± 18.4
Previous other antiplatelet medication plus CPG loading (300 mg), 29 (16%)	358.8 ± 63.0	271.7 ± 82.9	24.5 ± 19.2
Continued CPG medication for ≥7 days without loading, 21 (11%)	371.9 ± 45.1	230.0 ± 96.2	37.4 ± 26.3
<i>P</i> value ^a	.6388	.0091 ^b	.0013 ^b

^a One-way ANOVA.^b There was a significant difference between the first group and the third group on the Tukey-Kramer multiple comparison test ($P < .01$).**Table 5: Results of regression analysis for variables related to high PRU (>332)**

Variables	<i>P</i> Value	
	Simple Logistic Regression Analysis	Multiple Logistic Regression Analysis ^a
Gender	.001	.014
Age	.241	
Body weight	.009	.547
Mode of CPG medication	.096	.086
Combination therapy	.255	
Hypertension	.800	
Diabetes mellitus	.626	
Statin use	.598	
Smoking	.088	.114
Alcohol intake	.373	
Hematocrit level	.049	.169
Platelet count	.058	.141
Total cholesterol level	.443	
Triglyceride level	.159	
HDL cholesterol level	.287	
LDL cholesterol level	.499	

^a Variables with $P < 0.10$ were entered into multivariate analysis to determine their independent association with high PRU.

CPG the day before the coil embolization at the time of admission. If we have confirmatory evidence that CPG medication does not add bleeding risk in patients with unruptured intracranial aneurysms, then we may favor extended duration of medication for them in the preinterventional period. When we performed regression analyses with variables in relation to a high PRU value (>332), female sex was found to be the single significant factor (Table 5). A previous study also documented a similar tendency of different responses to CPG according to sex (men versus women, 200 ± 77 versus 220 ± 82 PRU, $P = .041$).³² The authors speculated that sex-specific differences in the cytochrome P450 system could have an influence on the formation of active metabolites of CPG.³²

What can be done in the high-risk patients in terms of antiplatelet premedication? We propose 2 solutions: 1) to increase the CPG dosage, and 2) to administer another antiplatelet agent. In a recent study comparing the impact of a high maintenance dose of CPG (150 mg/day) and the addition of cilostazol (a selective inhibitor of phosphodiesterase type 3), the latter was found to be superior in decreasing platelet aggregation and increasing percentage inhibition of P2Y₁₂ reaction units.³³ Prasugrel, a third-generation thienopyridine, might be another option. This was found to be associated with significant reduction in rates of ischemic events, but with increased risks of major bleeding and fatal bleeding in patients with acute coronary syndromes.³⁴ Temporary short-term administration of prasugrel during the periprocedural period might result in decreased procedure-related thromboembolic

events in patients undergoing coil embolization for unruptured intracranial aneurysms.

Apart from our study, genetic analyses, including cytochrome P450 2C19 polymorphisms, would be an alternative way to predict the CPG responsiveness.^{35–37} We need to choose the more cost-effective and timely way of predicting individual responses to antiplatelet prophylaxis. We might be able to restrict the patients being tested by using the VerifyNow P2Y₁₂ assay before gene studies.

Conclusions

The VerifyNow P2Y₁₂ assay seems to identify high-risk patients when we administer prophylactic antiplatelet agents before coil embolization of unruptured intracranial aneurysms. In our series, the patients in the fourth quartile PRU values (PRU > 332) showed a significantly higher rate of procedure-related thromboembolic events. Further study including a larger number of patients is expected to confirm this finding.

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