ORIGINAL PAPER

Nagoya J. Med. Sci. **80**. 207–215, 2018
doi:10.18999/nagjms.80.2.207

Association between CYP2C19 genotype and the additional effect of cilostazol to clopidogrel resistance in neuroendovascular therapy

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ABSTRACT

We investigated the association between *CYP2C19* genotype and additional effect of cilostazol on clopidogrel resistance (CR) in neuroendovascular therapy. Between January 2012 and January 2016, 447 consecutive patients were administered with 75-mg cilostazol/day. The VerifyNow System was used for evaluating P2Y12 reaction units (PRU) > 230 and/or percentage inhibition of platelet function (% Inhibition) ≤ 20 as CR. Among 158 patients with CR, 31 were administered with additional 100- or 200-mg cilostazol/day and their platelet function was evaluated. According to *CYP2C19* genotypes revealed using the Spartan RX and DNeasy Blood & Tissue Kit, patients were classified into three phenotypic groups: extensive metabolizer (EM, three patients), intermediate metabolizer (IM, 12 patients), and poor metabolizer (PM, 16 patients). Administration of additional cilostazol decreased PRU (EM group: 160.7 ± 85.2 after vs 278.3 ± 40.1 before, $P = 0.15$; IM group: 205.6 ± 74.0 vs 254.3 ± 35.0, $P = 0.02$; and PM group: 227.8 ± 52.2 vs 282.1 ± 30.4, $P = 0.003$), and increased % Inhibition (EM group: 40.0 ± 27.9 vs 9.3 ± 3.8, $P = 0.25$; IM group: 31.4 ± 18.0 vs 11.8 ± 8.2, $P = 0.001$; and PM group: 24.6 ± 15.0 vs 10.4 ± 9.3, $P = 0.001$). However, the rate of normalized-clopidogrel response, thromboembolic lesions, and bleeding complications were not significantly different among the three groups. Thus, the addition of cilostazol was effective on CR in terms of PRU, % Inhibition, rate of change of normalized-clopidogrel response, thromboembolic events, and bleeding complications irrespective of phenotype.

Keywords: *CYP2C19* genotype, cilostazol, clopidogrel resistance, endovascular treatment, VerifyNow System

Received: October 10, 2017; accepted: December 11, 2017

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INTRODUCTION

The implication of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel has been well recognized in neuroendovascular therapy to prevent thromboembolic events. However, clopidogrel resistance is often associated with an increased risk of thromboembolic complications.[1-5] Moreover, a loss-of-function (LOF) polymorphism in cytochrome P450 2C19 (*CYP2C19*) has been associated with clopidogrel resistance.[6-8]

Recently, the addition of cilostazol to DAPT has been reported to inhibit platelet activation and improve clinical outcomes following PCI.[9] Furthermore, in neuroendovascular therapy, it has been reported that adjunctive cilostazol (triple antiplatelet therapy) in clopidogrel resistant patients reduces the rate of clopidogrel resistance and suppresses new ischemic lesions without hemorrhagic complications compared with DAPT in carotid artery stenting.[10,11] However, the relationship between *CYP2C19* genotypes and the additional effect of cilostazol to clopidogrel resistance has not been elucidated.

Therefore, this study aimed to investigate the association between the additional effect of cilostazol to clopidogrel resistance and *CYP2C19* genotypes.

MATERIALS AND METHODS

Study Design

A total of 447 consecutive patients undergoing neuroendovascular therapy stent placement for carotid artery stenosis or vertebral artery stenosis and coiling for an intracranial aneurysm at Nagoya University Hospital for Neurosurgery between January 2012 and January 2016 were enrolled in the study. All patients received clopidogrel before the procedure and were tested for clopidogrel resistance using the VerifyNow System (Accriva Diagnostics, San Diego, California). Furthermore, the addition of cilostazol in patients with clopidogrel resistance was targeted. Patient background characteristics, diagnosis, procedure methods, intraprocedural complications, and diffusion-weighted imaging performed within 5 days were recorded and maintained in the database. *CYP2C19* genotypes were evaluated using Spartan RX (Spartan Bioscience Inc. Ottawa, ON, Canada) and the DNeasy Blood & Tissue Kit (QIAGEN, Hilden, Germany), and phenotypes were classified as extensive metabolizer (EM), intermediate metabolizer (IM), poor metabolizer (PM) from the genotypic data.

Patient Background Characteristics

We examined patients' medical history for diabetes mellitus, hypertension, and dyslipidemia, which are risk factors of cerebrovascular disease. Diabetes mellitus was defined as hemoglobin A1c level of ≥ 6.5 % or as patients undergoing diabetes treatment. Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg or a diastolic blood pressure of ≥ 90 mmHg or patients on antihypertensive medication. Dyslipidemia was defined as a low-density lipoprotein cholesterol level of ≥ 140 mg/dL or patients on statin.

Evaluation of Platelet Function

Platelet function was analyzed using the VerifyNow System. VerifyNow-P2Y12 assay results are expressed in P2Y12 Reaction Units (PRU) and % inhibition of platelet function from baseline activation via thrombin receptor activating peptide (% Inhibition).[12] Clopidogrel resistance was defined as PRU > 230 or/and % Inhibition ≤ 20 according to previous studies.[2,5,13]

Medication Regimen

Patients were administered with a combination of clopidogrel 75 mg/day and aspirin 100 mg/day or clopidogrel 75 mg/day from three weeks before neuroendovascular therapy and analyzed by VerifyNow System from two weeks before the procedures. Patients were subsequently identified as clopidogrel resistant and were prescribed with an additional cilostazol 100 mg/day or 200 mg/day at the discretion of surgeons. After approximately two weeks, the effect of the drug was measured again with VerifyNow System. In Japan, the recommended dose of cilostazol is 200 mg/day. However, in our study cilostazol, 100 mg/day was selected as the dose as the patient receiving cilostazol 200 mg/day was presented with a headache or tachycardia.

Genotype Data

Spartan RX and the DNeasy Blood & Tissue Kit were used for the genotypic analysis. Spartan RX is portable technology enables healthcare personnel with no previous training in genetic laboratory techniques to undertake genotyping.[14,15] DNeasy Blood & Tissue Kit extracts genomic DNA from the samples by proteinase K digestion in combination, following the tissue protocol. We referred to some previous reports,[7,16] and defined EM as CYP1C19*1/*1, IM as CYP2C19*1/*2 or CYP2C19*1/*3, and PM as CYP2C19*2/*2 or CYP2C19*2/*3 or CYP2C19*3/*3.

Statistical Analysis

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[17] EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics. Continuous variables were presented as mean ± standard deviation. The relationship between the results of before and after the addition of cilostazol to clopidogrel was evaluated using a paired *t* test. However, as PRU and % Inhibition of EM group were not normally distributed, we used Wilcoxon signed rank test. To analyze significant differences among the three phenotype groups (EM group, IM group, and PM group), we compared categorical variables using Fisher's exact test applying Bonferroni correction method and assessed continuous variables using one-way ANOVA. $P < 0.05$ was considered statistically significant.

RESULTS

The genotypic analysis of 447 patients undergoing neuroendovascular therapy with clopidogrel 75 mg/day was analyzed using VerifyNow platelet function assay.

Among the 447 patients tested using the VerifyNow System, a total of 158 were diagnosed with clopidogrel resistance. A total of 32 patients were administered with cilostazol. Among these, *CYP2C19* genotypic analysis was performed on 31 patients. We could not analyze *CYP2C19* genotypic analysis in the remaining single patient because the patient moved to other hospital. The genotypes were distinguished into the following the three groups: EM group (n = 3), IM group (n = 12), and PM group (n = 16) (Fig. 1). There were no newly added drugs other than cilostazol during this study. No significant difference was found in the respective baseline demographic or medical history characteristics before the addition of cilostazol to clopidogrel resistance among the three groups (Table 1).

Results of PRU before and after the addition of cilostazol to clopidogrel resistance revealed that PRU after the addition of cilostazol was significantly lower than PRU before the addition of cilostazol in the IM and PM groups (IM group: 205.6 ± 74.0 vs 254.3 ± 35.0, $P = 0.02$ and

Table 1 Baseline characteristics before addition of cilostazol

	Phenotype			p-value
	EM (n = 3)	IM (n = 12)	PM (n = 16)	
General characteristics				
Age ± SD	69.3 ± 5.9	64.1 ± 10.9	63.9 ± 8.8	0.65
Female (%)	3 (100)	7 (58.3)	11 (68.8)	0.55
Risk factors				
Diabetes mellitus (%)	1 (33.3)	3 (25.0)	0 (0)	0.07
Hypertension (%)	3 (100)	8 (66.7)	14 (87.5)	0.32
Dyslipidemia (%)	1 (33.3)	5 (41.7)	7 (43.8)	1
Medications				
ARB and/or CCB (%)	3 (100)	8 (66.7)	14 (87.5)	0.32
Statin (%)	1 (33.3)	5 (41.7)	7 (43.8)	1
Diagnosis				
Aneurysm (%)	3 (100)	7 (58.3)	12 (75.0)	0.45
ICS (%)	0 (0)	4 (33.3)	4 (25.0)	0.84
VAS (%)	0 (0)	1 (8.3)	0 (0)	0.47
VerifyNow assay				
% Inhibition ± SD	9.3 ± 3.8	11.8 ± 8.2	10.4 ± 9.3	0.88
BASE ± SD	307.7 ± 42.6	288.2 ± 29.9	312.5 ± 48.0	0.31
PRU ± SD	278.3 ± 40.1	254.3 ± 35.0	282.1 ± 30.4	0.1

Note: Values are expressed as numbers (%) or mean ± SD.
Abbreviations: EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; ICS, internal carotid artery stenosis; VAS, vertebral artery stenosis; % Inhibition, percentage inhibition of platelet function; BASE, baseline results; PRU, P2Y12 reaction units; and SD, standard deviation.

PM group: 227.8 ± 52.2 vs 282.1 ± 30.4, $P = 0.003$) (Fig. 2A). In the EM group, PRU after the addition of cilostazol to clopidogrel resistance did not differ significantly from PRU before the addition of cilostazol (160.7 ± 85.2 vs 278.3 ± 40.1; $P = 0.15$); however, the rate of change in PRU in the EM group was higher than that in the IM and PM groups.

As illustrated in Fig. 2B, % Inhibition after the addition of cilostazol to clopidogrel resistance was significantly higher than that before the addition of cilostazol to clopidogrel resistance in the IM and PM groups (IM group: 31.4 ± 18.0 vs 11.8 ± 8.2, $P = 0.001$ and PM group: 24.6 ± 15.0 vs 10.4 ± 9.3, $P = 0.001$). The % Inhibition after the addition of cilostazol to clopidogrel resistance was not significantly different from that before the addition of cilostazol to clopidogrel resistance in the EM group (40.0 ± 27.9 vs 9.3 ± 3.8, $P = 0.25$); however, the rate of change

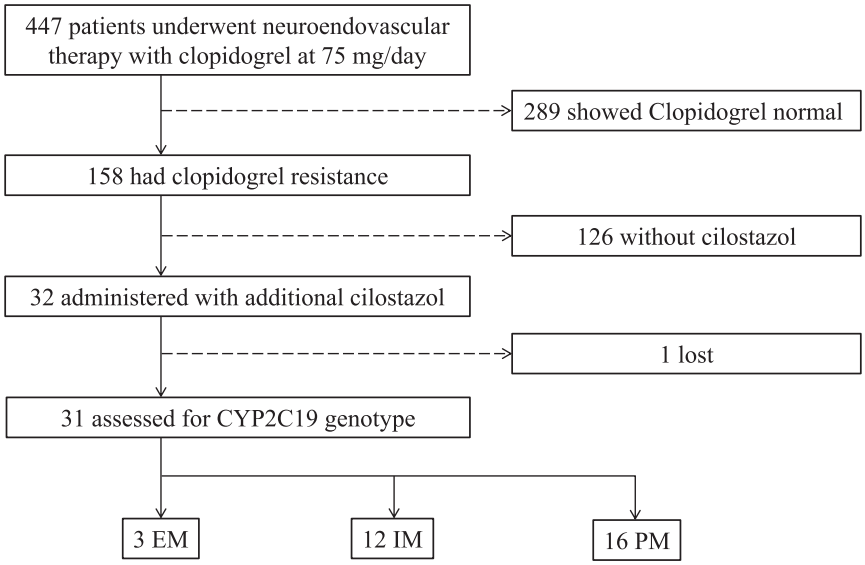

Fig. 1 Flow chart of study patients

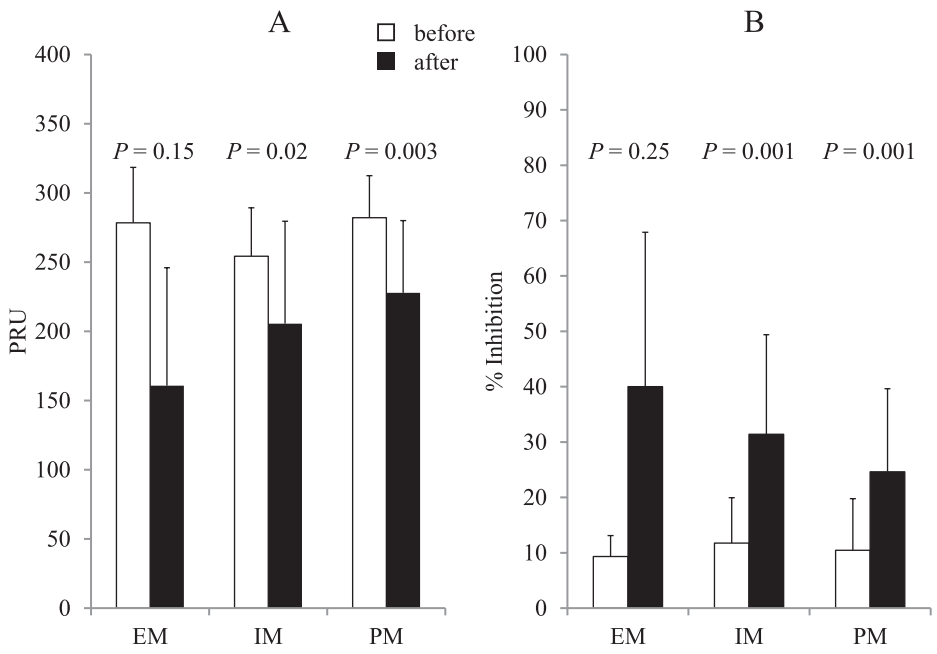

Fig. 2 Results of PRU before and after the addition of cilostazol to clopidogrel resistance (A) and % Inhibition (B). Results are expressed as mean (boxes) ± SD (error bars).
Abbreviations: % Inhibition, percentage inhibition of platelet function; PRU, P2Y12 reaction units; SD, standard deviation

Table 2 Post procedural complications

	Phenotype			P value
	EM (n = 3)	IM (n = 12)	PM (n = 16)	
Normalized-clopidogrel response (%)	1 (33.3)	7 (58.3)	6 (37.5)	0.51
Thromboembolic lesions (%)	3 (100)	9 (75.0)	9 (56.2)	0.34
Bleeding complications (%)	0 (0)	1 (9.1)	3 (18.8)	0.76

Abbreviations: EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer

of % Inhibition between before and after the addition of cilostazol to clopidogrel resistance in EM group was higher than that in the IM and PM groups.

Normalized-clopidogrel response was observed in 1/3 patients (33.3%) in the EM group, in 7/12 patients (58.3%) in the IM group, and in 6/16 patients (37.5%) in the PM group (Table 2). The ratio of the patients with a normalized-clopidogrel response after the addition of cilostazol was not significantly different among the three groups.

There was no significant difference in thromboembolic lesions and bleeding complications in each group (Table 2). However, one patient in the PM group had transient thalamic aphasia as an ischemic event, which was completely recovered.

DISCUSSION

Two important clinical findings were discovered. First, irrespective of *CYP2C19* genotype, the addition of cilostazol to clopidogrel significantly decreased the PRU and increased the % Inhibition. Second, there was no significant difference in the prevalence of thromboembolic events and bleeding complications among the *CYP2C19* genotypes with the addition of cilostazol to clopidogrel resistance.

Previously, it was demonstrated that the addition of cilostazol to clopidogrel resistance decreased PRU and increased % Inhibition.[10,18-20] However, the relationship between *CYP2C19* genotypes which is one of the factors responsible for clopidogrel resistance and effect of the addition of cilostazol remains unclear.[10,18-20] Particularly, PM usually demonstrates a significant reduction in platelet inhibition, patients in the PM group are likely to become clopidogrel resistant.[7,21-23] In the present study, the PM group exhibited the highest frequency of clopidogrel resistance. However, after the addition of cilostazol, the frequency of normalized-clopidogrel response did not differ significantly among all the groups. Therefore, this study indicated that the addition of cilostazol to clopidogrel resistance was effective in particular patients with a PM.

Several reports have suggested that clopidogrel resistance was associated with the increased periprocedural thromboembolic events in neurovascular therapy.[1-5] Conversely, reduced rate of thromboembolic events without increasing the rate of bleeding complications was also reported after the addition of cilostazol to clopidogrel resistance.[10,11] In the present study, there was no significant difference in the thromboembolic events and the bleeding complications among all groups classified by *CYP2C19* genotypes. Therefore, the results indicated that the addition cilostazol to clopidogrel resistance irrespective of *CYP2C19* genotypes prevented the thromboembolic events without bleeding complications.

Clopidogrel is metabolized to active thiol metabolite in the liver in two oxidation stages which involve several CYP enzymes; CYP2C19 particularly plays a significant role in this conversion. When the active thiol metabolite inhibits binding of adenosine diphosphate (ADP) to

the P2Y12 receptor, the synthesis of cyclic adenosine monophosphate (cAMP) is promoted. As a consequence, the activity of platelet aggregation is blocked.[20,24] Thus, *CYP2C19* LOF alleles, which exhibit a poor metabolic function, cause a reduction in the formation of active thiol metabolite and lead to a lack of platelet aggregation inhibition. However, a part of cilostazol is metabolized in the liver by P450 enzymes, and cilostazol enhances cAMP within the platelets by blocking phosphodiesterase-3A.[19,25] These mechanisms explained that the addition of cilostazol to clopidogrel augment platelet aggregation inhibition. Because cilostazol alone cannot affect ADP and P2Y12 receptor, these mechanisms cannot explain the changes in PRU and % Inhibition after the addition of cilostazol to clopidogrel in the present study. Kim *et al.* suggested that the additional effect of cilostazol to clopidogrel was maximized in patients in the PM group of genotype CYP3A5*3/*3 owing to the lack of decrease in the concentration of the thiol metabolite by cilostazol in CYP3A5*3/*3 carriers.[26] Future studies are required to clarify the mechanism that is not influenced by *CYP2C19* genotypes.

The present study has several limitations. First, it was performed using a small sample size, specifically in the EM group, and it also lacked a comprehensive prospective design. Second, the decrease in the risk of thromboembolic events owing to the addition of cilostazol to clopidogrel is unclear because the results were not directly compared with clopidogrel resistance.

Therefore, a prospective, multi-center study is suggested in the future to further confirm the efficacy of addition of cilostazol to clopidogrel resistance.

CONCLUSIONS

In conclusion, this study provided novel and important information regarding the additional effect of cilostazol to clopidogrel resistance. The results also demonstrated that lower PRU and higher % Inhibition and the rate of change of normalized-clopidogrel response, thromboembolic events, and bleeding complications were not associated with *CYP2C19* genotypes.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ACKNOWLEDGEMENTS

I am grateful to all participants of the study.

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