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Original Article

Association of Polymorphisms in CYP2C19 with the Efficacy of Clopidogrel Therapy in South Indian Patients Undergoing Percutaneous Coronary Intervention

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ABSTRACT

Background: The dual antiplatelet therapy (DAPT) with aspirin and clopidogrel has been considered as the standard of care in the setting of acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI). Recent evidence supports a role of loss-of-function (LOF) variants in the CYP2C19 as a determinant of clopidogrel response. Carriers of the CYP2C19*2 LOF allele has found to have the reduced pharmacodynamic response to clopidogrel and worse clinical outcome as compared with non-carriers in Asian countries including Indian population. However, it is unknown whether the time course of the antiplatelet effects of clopidogrel differs according to CYP2C19 genotype in South Indian patients with ACS. **Methods:** We assessed the platelet reactivity in the early and late phases of ACS according to CYP2C19 genotypes. Eighty six consecutive in-patients who were admitted with ACS at our center were enrolled in the study. The determination of platelet aggregation was done by using a platelet aggregometer and genetic analysis was done by PCR-RFLP method. **Results:** The numbers of patients carrying the CYP2C19*1/*1 (extensive metabolizer, EM), *1/*2 (Intermediate metabolizer, IM), *2/*2 (poor metabolizer PM), genotypes were 22 (30.9%), 37 (52.1%), 12 (16.9%), respectively. Time course of platelet aggregation from baseline to the late phase among the 3 genotypes indicate that there was statistically significant at 30th day of treatment (p=0.004) between wild versus hetero and homozygous variant alleles. The percentage of patients shifted to prasugrel from clopidogrel due to non-response were 4 (8%), 11(29%), 6 (50%) in wild, heterozygous and homozygous variant alleles. In homozygous group, we found 4 out of 6 patients developed acute stent thrombosis within one week of PCI. **Conclusion:** We observed that the CYP2C19*2 and CYP2C19*1/*2 are the major determinants of clopidogrel efficacy. Acute stent thrombosis was observed in patients carrying CYP2C19*2 variant allele
Keywords: Antiplatelet therapy, Acute coronary syndrome, Percutanous coronary intervention, Clopidogrel, Pharmacogenetics.

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INTRODUCTION

The dual antiplatelet therapy (DAPT) with aspirin and clopidogrel has been widely implicated in the treatment for acute coronary syndromes (ACS) or patients undergoing percutaneous coronary intervention (PCI).[1-2] However, it is characterized by high inter-individual variability in clinical response.[3] Inadequate dosing of clopidogrel is found to be associated with adverse cardiovascular events, including stent thrombosis after implantation.[4-5] Clopidogrel is a pro-drug that must be metabolized by the cytochrome P (CYP) 450 enzyme system to generate active metabolites.[6] Metabolic activation by CYP2C19 is crucial for the generation of such metabolites. Several gene variants are associated with the reduced or enhanced CYP2C19 activity.[7-9] Furthermore, the allelic frequencies of CYP2C19 variants show significant inter-ethnic differences.[10] The allele frequencies of CYP2C19*2, CYP2C19*3 and CYP2C19*17 have found to be 0.280, 0.065 and 0.010 (rare) for Chinese, 0.310, 0.050 and 0.025 for Malays, and 0.375, 0.010 (rare) and 0.165 for Indians.[10] In a study from south India, it was reported the high prevalence (66%) of CYP2C19*2 variant allele.[11] In a study from north India, it was shown that allele frequency of CYP2C19*1 and *2 was 0.7 and 0.3 whereas CYP2C19*3 allele was absent in north Indians[12] whereas very low frequency was reported in south Indian population (2%).[13] This indicates that individuals carrying CYP2C19*2 or *3 or both are more likely to be resistant to clopidogrel. CYP2C19*17 is associated with rapid metabolism of clopidogrel.[14] In Indian population the reported frequency CYP2C19*17 are in between 16% - 35.5%.[7-10-14,15] Studies have shown that CYP2C19*17 variant is not independently associated with clopidogrel response and observed effect of this variant is due to LD with the CYP2C19*2 loss-of-function variant.[16]

Several cohorts studies have found that patients with the CYP2C19*2 or CYP2C19*3 allele who have undergone PCI are more likely to experience worse clinical outcomes during clopidogrel therapy.[17-20] Similarly in a study of acute ischemic stroke, it was also reported that patients with CYP2C19 LOF alleles have a reduced response to clopidogrel and found poorer outcome even up to 6 months after stroke.[21] The carriers of a CYP2C19*2 LOF have found to have significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and a higher rate of major adverse CV events.[17-22] In a study by Shalia *et al*, have observed that poor response to clopidogrel at 24 h with the variant genotypes of CYP2C19*2 as compared to wild type.[14] In one study, it has been reported that genetic contribution accounts for only approximately 12% of the response variability to clopidogrel.[18] However, it is unknown whether the time course of the antiplatelet effects of clopidogrel differs according to CYP2C19*2 phenotype in south Indian patients with ACS. We serially assessed the platelet reactivity in the early and intermediate phases of acute coronary syndrome (ACS) patients according to CYP2C19 genotype.

MATERIAL AND METHODS

Study subjects

Eighty six (86) consecutive in-patients who were admitted with acute coronary syndrome at our centre were enrolled in our study. The Institu-

tional Ethical Committee has approved the study and informed consent from each patient was obtained. Out of 86 patients, the data of 71 patients were finally analysed as the genetic analysis data was not available in 15 cases (Figure 1). Standard definitions of ACS as defined by ACC guidelines were used in the study to include the patients. The baseline demographic and clinical details were recorded in a standard format. Patients with major bleeding events within 7 days before enrolment, hematologic, kidney, liver or malignant disease, or the use of oral anticoagulant agents were excluded from the study. All patients were required to receive aspirin 100 mg/day indefinitely and a 600-mg loading dose of clopidogrel followed by 75 mg/day. Primary PCI was performed immediately after a loading dose of clopidogrel. All coronary angiograms were evaluated by a single cardiologist who was blinded to all other clinical and genetic data. Follow-up visits were conducted at participating centre for one year. Patients who became unable or were unwilling to come to the hospital were contacted by telephone.

Platelet Aggregation Test

The determination of platelet aggregation was done by using a platelet aggregometer (Chronolog) by the turbidimetric method, using 10 µM of adenosine diphosphate (ADP) as per the procedure previously described by our group.[23] The platelet aggregation test was performed in all the 71 patients at 0 (baseline), 7th and 30th day of treatment with aspirin and clopidogrel.

Genetic analysis of CYP2C19*2 by PCR-RFLP technique

Five ml of venous blood was collected from all the subjects in EDTA vacutainer. Genomic DNA was isolated by salting out procedure. Specific primers were designed for CYP2C19*2 SNP by using primerblast tool. PCR was carried out with forward primer 5'-CAACCAGAGCTTGGCATATTG-3', Reverse primer 5'CACAAATACGCAAG CAGTCAC-3' in 10 µL reaction. PCR conditions were followed: Initial denaturation at 94°C for 4 min, denaturation at 94°C for 30 sec, annealing at 60°C for 30 sec, extension at 72°C for 45 sec for 35 cycles followed by final extension at 72°C for 7 min. 300 bp length PCR product was subjected to restriction fragment length polymorphism (RFLP) with 1 unit of *SmaI* (New England Biolabs) enzyme with 3 hr of incubation at 25°C. Products were evaluated on 2% agarose gels stained with Ethidium Bromide. GG (wild) allele gives bands at 187 bp and 113 bp, while hetero (GA) allele gives bands at 300 bp, 187 bp and 113 bp, where mutant (AA) allele lacks restriction site and gives undigested band at 300 bp. PCR -RFLP was carried out with both positive and negative controls, 20% of randomly selected samples were repeated to check reproducibility (Figure 2).

Clinical Outcomes

All the patients were monitored for one year after PCI and clinical end-points were noted.

Adverse cardiovascular events were defined as death from cardiovascular causes, spontaneous myocardial infarction, stent thrombosis, ischemic stroke, target vessel revascularization, or non-target vessel revascularizations were recorded as primary end-points.

Statistical Analysis

The data are presented as the mean ± SD. Furthermore, the data were compared using one-way ANOVA test. Categorical variables are expressed as percentages and were compared using the chi-square test or Fisher's exact test. A $p<0.05$ was considered statistically significant. Data were analyzed with SPSS 19 software.

RESULTS

The number of patients carrying the CYP2C19*1, *1/*2, *2/*2, genotypes were 22 (30.9%), 37 (52.1%), 12 (16.9%), respectively. The demographic, clinical manifestations and angiographic findings of all patients were stratified according to three genotypes and were shown in Table 1. There was no statistical significance in the demographic, clinical manifestations and angiographic findings among all the genotypes were observed except for the frequency in RCA lesion ($p = 0.03$). Similarly, there were no significant difference in haemoglobin, platelet count and serum creatinine, usage of drugs like aspirin, clopidogrel, calcium channel blocker, statins was observed among all the three genotypes except for beta blockers ($p = 0.05$) (Table 2).

Platelet Aggregation

Platelet reactivity was serially assessed in 71 patients with ACS who underwent stent implantation and received aspirin and clopidogrel. The percentage of platelet aggregation was measured at baseline, 7th and 30th day of aspirin and clopidogrel treatment and results are shown in (Figure 3). Platelet aggregation levels at baseline were not significant among the 3 genotypes i.e., wild allele (CYP2C19*1), heterozygous variant allele (CYP2C19*1/*2), homozygous variant allele (CYP2C19*2) are 53 ± 25, 71 ± 20 and 72 ± 34 percent respectively. The platelet aggregation from baseline to one week among the 3 genotypes indicate that there was

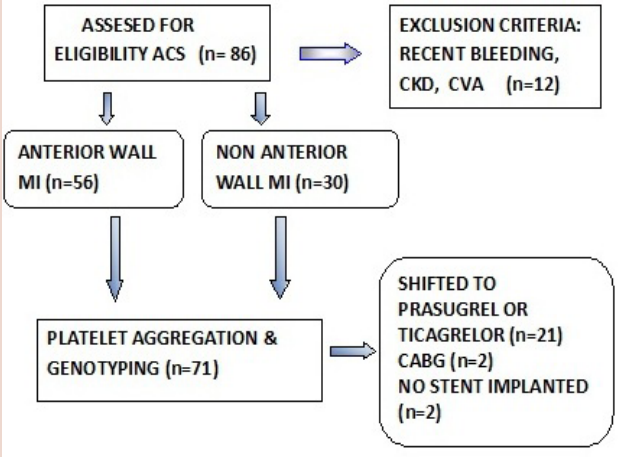

Figure1: Flow chart describing the subject recruitment, treatment and analysis.

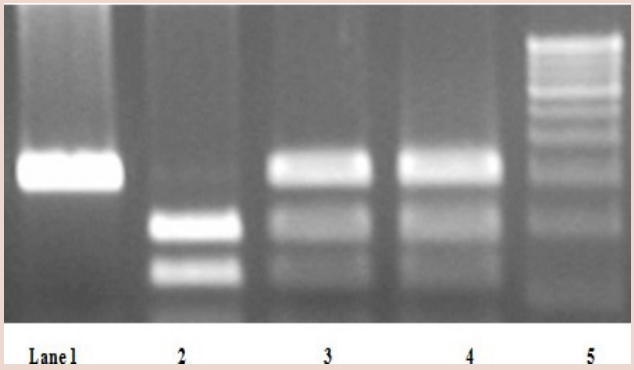

Figure 2: Representative gel picture of CYP2C19 analysed by PCR-RFLP method.

Lane 1: CYP2C19*/2*2(300 bp); Lane 2: CYP2C19*1/*1(187 bp and 113 bp); Lane 3 & 4: CYP2C19*1/*2 (300bp, 187bp & 113bp); Lane 5: DNA marker, 100bp.

Table 1: Baseline characteristics of subjects according to genotype

VARIABLE	CYP2C19*1 (n=22)	CYP2C19*l/*2 (n=37)	CYP2C19*2 (n=12)	P value
Age inyrs (mean ± SD)	56.05 ± 9.34	55.78 ± 11.17	54.83 ± 13.29	0.95
Body Mass Index (Kg/m²)	25.65 ± 3.73	25.31 ± 3.38	25.47 ± 4.64	0.96
Hypertension	59%	48.60%	83.33%	0.1
Diabetes	50.00%	45.90%	58.00%	0.76
Hypothyroidism	4.50%	2.70%	8.30%	0.7
Smokers	54%	48%	58%	0.81
Previous MI	4.50%	2.70%	8.30%	0.7
Vessel Treated				
LAD	50.00%	29.00%	41.00%	0.29
LCX	31.00%	16.00%	16.00%	0.34
RCA	50.00%	21.00%	16.00%	0.03
Syntax Score	16	20	19	0.25
Total Stent Length	9.7 ± 2.6	15.56 ± 5.9	11.83 ± 1.7	0.2
Stent Diameter	2.4 ± 2.1	2.9 ± 2	2.7 ± 2.3	0.32

LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery

Table 2: Clinical laboratory parameters and percentage of subjects on various drugs: Data is Distributed according to genotype

Parameter	CYP2C19*1 (n=22)	CYP2C19*l/2 (n=37)	CYP2C19*/2 (n=12)	P value
Hemoglobin (gm/dl)	12.89 ± 45.2	13.26 ± 2.3	13.3 ± 6.04	0.92
Platelet Count (x10⁹/L)	2.44 ± 0.95	2.3 ± 1.2	2.5 ± 1.04	0.9
Seram Creatinine (mg/dl)	1.04 + 0.09	1.1 ± 0.2	1.1 ± 0.3	0.84
Aspirin+				
Clopidogrel	68%	81%	75%	0.54
CCB	4.50%	5.40%	0	0.72
Beta Blockers	45%	70%	83%	0.05
ACEI	72%	70%	83%	0.68
Atorvastain	31%	29%	60%	0.62
Rosuvastain	68%	70%	75%	0.91

CCB, calcium channel blockers; ACEI, angiotensin converting enzyme inhibitor

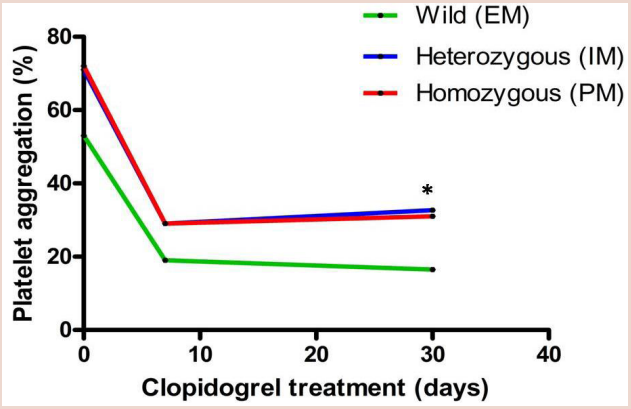

Figure 3: Platelet aggregation according to CYP2C19* genetic variants. Platelet aggregation test was done at baseline (0 days), 7th day and 30th day of clopidogrel treatment and data was stratified according to CYP2C19*1/*1 (wild, EM), CYP2C19*1/*2 (heterozygous, IM) and CYP2C19*2/*2 (homozygous, PM) (*p=0.04).

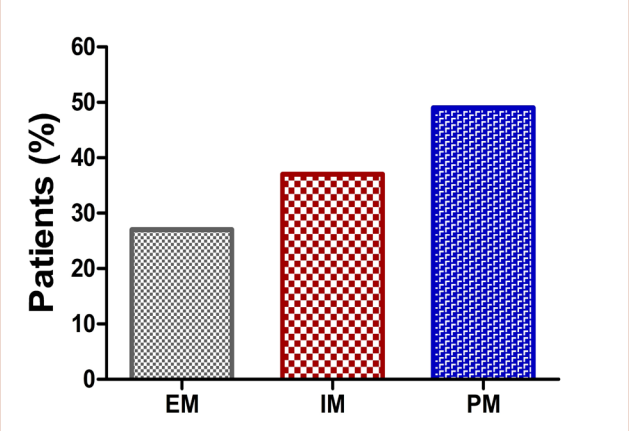

Figure 4: Percentage of patients shifted to alternative therapy (Prasugel) in patients carrying, EM (Extensive metabolizer, wild); IM (Intermediate metabolizer, heterozygous);PM (poor metabolizer homozygous).

no statistically significant difference among all thee genotypes (p=0.12), whereas at 30th day, the platelet aggregation were 16.59 ± 14.98, 32.7 ± 17.46, 31.75 ± 19.79 percent respectively which is statistically significant among the patients carrying wild allele compared to patients carrying heterozygous and homozygous alleles (p=.004).

Clopidogrel Resistance

Clopidogrel resistance is a pharmacodynamics phenomenon where there is no significant change in platelet function after treatment as compared to the baseline. In studies employing light transmittance aggregometry, as in the present study, a change in maximal aggregation ≤10 percent from baseline, using ADP as the agonist, is defined as "resistance.[24] In the present study, during the follow up period the percentage of patients shifted to prasugrel from clopidogrel due to non-response were 4 (8%), 11(29%), 6 (50%) in wild, heterozygous and homozygous variant alleles respectively (Figure 4). In homozygous group, we found 4 out of 6 patients developed acute stent thrombosis within one week of PCI.

DISCUSSION

In this study, the association between CYP2C19 polymorphisms and the clinical efficacy of clopidogrel therapy in patients from south India who had undergone PCI was studied. Among the studied subjects, the allelic frequency of CYP2C19*1, *1/*2, *2 were 30.9%, 52.1%, and 16.9% respectively, indicating the higher requency of CYP2C19 1*/2* in patients with ACS. The variant allele frequency of CYP2C19*2 was found to be 35.2% in Eastern India population[17] and 37.9% was reported in south Indian Tamilian population.[25] In a recent study in Chinese population, the allelic frequency of CYP2C19*2 and *3 are 31.80 and 5.06% respectively.[26] Previous studies have shown that the allelic frequency of CYP2C19*2 and *3 in Asian populations are 30%, and 10%[27,28] and in Caucasian and African-American populations the allelic frequency of CYP2C19*2 genotype are 13% and 18%[27,28] respectively.

Next, we determined whether the effects of the CYP2C19 variants on the ADP-stimulated platelet. Aggregation before, one week and one month of clopidogrel treatment. Patients carrying CYP2C19*1*/2 or CYP2C19*2 variant allele was found to be significantly associated ADP-stimulated platelet aggregation suggesting that the CYP2C19*1*/2 or CYP2C19*2 variant are the main determinant of clopidogrel efficacy. Though not statistically significant, we found decreased baseline platelet aggregation in patients carrying either CYP2C19*1*/2 or CYP2C19*2 variant allele as compared to patients carrying wild allele. The reason for this difference is not known. Even though the CYP2C19*2 and *3 LOF alleles have been reported, the CYP2C19*2 allele is the most common type among the reduced-function genes and has been shown as a prime indicator of low response to clopidogrel in many studies.[28,29] Poor metabolizers (CYP2C19*2) with ACS or undergoing PCI intervention treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function[7]. Similarly, IM (e.g., *1/*2, *1/*3) have higher on-treatment residual platelet activity on average as compared with EM, hence the patients with ACS or undergoing PCI, CYP2C19*1/*2 heterozygotes treated with clopidogrel have increased risks for serious adverse cardiovascular outcomes, including stent thrombosis.[7]

In the current study, we found that the percentage of patients shifted to prasugrel from clopidogrel due to non-response are 8%, 29%, 50% in wild, heterozygous (IM) and homozygous variant (PM) alleles respectively, indicating that majority of the patients carrying PM or IM phenotypes require shifting of alternative drug since they found to have resistant to clopidogrel. Studies have shown up to 30% of patients on conventional dose of clopidogrel exhibit an inadequate antiplatelet response, otherwise called as clopidogrel resistance.[30,31] Patients with laboratory-defined resistance have shown increased risk of atherothrombosis.[32,33]

In the present study, we observed that in homozygous variant (PM) group, 4 out of 6 patients developed acute stent thrombosis within one week of PCI. In a study by Zhu *et al*, in Chinese patients showed that the CYP2C19 LOF alleles (*2 and *3) are risk factors for the prognosis of patients who have undergone carotid artery stenting and are on clopidogrel therapy.[26] In the same study, they observed that two patients carrying LOF alleles developed stent thrombosis. In a recent meta-analysis demonstrated that the presence of even one reduced function of CYP2C19 allele was associated with a significant increased risk of adverse cardiovascular events particularly stent thrombosis in patients who receive clopidogrel[34]. Studies have shown that more episodes of stent thrombosis occurred in first 30 days of stent implantation and the results of recent clinical trials suggest that intensive platelet inhibition is prerequisite to prevent cardiovascular events.[17-35]

Based on our results and findings from the several studies, it is conceivable that genotyping will be beneficial to the patients who are on clopidogrel treatment.[36-38] The cost-effectiveness analysis based on the TRITON-TIMI 38 trial have suggested that genotyping patients before selecting antiplatelet treatment could offer more value in the clinical setting than putting on drug therapy without regard to pharmacogenomic test results.[36] In another study, Johnson *et al*, studied the budget analysis to estimate the financial impact of CYP2C19 testing in a cohort of ACS/PCI patients being treated with clopidogrel, prasugrel, or ticagrelor, and observed the genetic testing is more cost-effective than patients treated with either prasugrel or ticagrelor.[37] In a recent study by Wang *et al*, suggested that CYP2C19*2 genotype-guided antiplatelet therapy remained a cost-effective approach as compared with the use of generic clopidogrel or ticagrelor in post-PCI ACS patient.[38] Based on these evidences, the value of genotyping reflects both fewer adverse events and lower costs to the patients.

There are several limitations in our study. Our study included a relatively small number of patients to evaluate clinical outcomes. The coexistence of other factors influencing clopidogrel induced platelet inhibition such as P2Y12 gene polymorphisms and other CYP2C19 LOF alleles have not been investigated in this study. A larger study involving patients with PCI on clopidogrel treatment, genotyping, monitoring the platelet aggregation testing for 6 to 12 months and study the clinical outcome warrants further investigation.

CONCLUSION

To conclude, consistence with the other studies, we also observed that the CYP2C19*2 and CYP2C19*1/*2 are the major determinants of clopidogrel efficacy. The majority of IM and PM have decreased platelet reactivity. Acute stent thrombosis was observed in patients carrying CYP2C19*2 variant allele.

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CONFLICT OF INTEREST

None.

ABBREVIATION USED

ACS: acute coronary syndrome; ADP: adenosine diphosphate; EDTA,: ethylenediaminetetraacetic acid; EM: extensive metabolizer; IM: intermediate metabolizer; LOF: loss of function; PCI: percutaneous coronary intervention; PCR: polymerase chain reaction; PM: poor metabolizer;

RCA: right coronary artery; RFLP: restriction fragment length polymorphism.

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