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CYP2C19 Genotypes and Stent Thrombosis: Is There a Correlation?

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ABSTRACT

Background: Clopidogrel is an inactive prodrug and becomes active by undergoing enzymatic reaction. We conducted a study to investigate the impact of genetic variation in metabolism of clopidogrel in patients with angiographically proven stent thrombosis compared to control population.

Methods: A total of 51 patients were included in the study between January 2011 and January 2013. Twenty six patients with angiographically proven cases of stent thrombosis were compared with matched post percutaneous coronary intervention patients treated during the same time period and had completed at least six month follow-up. Each group were evaluated in clinical parameters, investigation profile and allele specific PCR (AS-PCR) analysis (CYP2C19) of clopidogrel metabolism. Patients were classified as normal, intermediate or poor metabolisers from the for allele specific PCR analysis. Both the groups were compared using chi square test. P value < 0.05 was considered statistically significant.

Results: The mean age of the population was 56.08±8.48 and 59.28±9.16 for stent thrombosis and control group, respectively. In patients with stent thrombosis, prevalence of Intermediate metaboliser seen in 50 % (vs. 56% in control group p = 0.847), poor metaboliser seen in 42.30 % (vs. 4 % in control group, p = 0.004) and normal metaboliser seen in 7.69 % (vs. 40% in control group, p=.021). Mortality was seen only in 2 patients in stent thrombosis group having poor metaboliser genotype.

Conclusion: This data provide a little insight into the role of genetic testing for planning treatment of complex/high risk PCI. From the data, it can be concluded that stent thrombosis was more frequently associated with poor clopidogrel metaboliser's subgroup.

Key words: clopidogrel resistance; CYP2C19; PCI; stent thrombosis

INTRODUCTION

Dual-antiplatelet therapy (DAPT)is proven to be effective in preventing stent thrombosis to a greater extent. It is considered as standard of care in patients who underwent percutaneous coronary intervention (PCI). Despite the administration of DAPT, ST reported at a rate of 0.5-2% in elective cases and up to 6% in acute coronary syndromes(ACS) patients. [1,2]

Mechanism involving poor clopidogrel response is not clearly understood. Clopidogrel is an inactive pro-drug and CYP2C19 is one of the major enzymes involved in its metabolism. Thus, cellular or genetic factors are considered as responsible for poor metabolism of clopidogrel. [3] Functional polymorphisms in the CYP2C19gene result in highly variable enzyme activity. [4] Clopidogrel non-responsiveness is reported to vary between 4% to 44% among different populations. [5] Carriers of the CYP2C19*2 reduced function allele have significant reductions in platelet inhibition [6] and increased risk of adverse cardiovascular events with 3-fold increase in ST. [7] The aim of this study was to investigate the impact of genetic variation in metabolism of clopidogrel in patients with angiographically proven stent

thrombosis compared to control population (no reported stent thrombosis at 6 month follow-up).

METHODS

This was a single centre, observational study. Consecutive patients presented to our facility between January 2011 and January 2013 with angiographically proven cases of definite stent thrombosis were included in the 'stent thrombosis' arm of the study. During the same time period, matched post PCI patients who completed at least 6 months of follow-up were included the 'control' arm of the study. Their angiography and angioplasty reports were taken out from hospital records and reassessed. Patients who refused to provide informed consent were excluded from the study. The study protocol was approved by institutional ethics committee. Each group were evaluated in clinical parameters and investigation profile. On day 1 of recruitment in the study, samples for allele specific PCR analysis (CYP2C19) of clopidogrel metabolism were taken from both the groups. Patients in both the groups received DAPT (aspirin and clopidogrel), statin, angiotensin - converting enzyme inhibitors and beta-blockers as per standard guidelines.

Cytochrome-P19 (CYP2C19) genotyping for clopidogrel response was assessed for both the groups. According to allele specific PCR (AS-PCR) analysis individuals were stratified in one of these six(CYP2C19*1/*1, CYP2C19*1/*2 CYP2C19*1/*3, CYP2C19*2/*2, CYP2C19*2/*3 CYP2C19*3/*3) categories depending upon the presence or absence of the polymorphisms G681A and G636A. Patient were classified as poor metaboliser (2/2, 2/3, 3/3), intermediate metaboliser (1/2,1/3) and normal metaboliser(1/1).

Statistical Analysis

Continuous variables were presented as mean ± standard deviation and categorical variables were presented as frequency and percentage. Both the groups were compared using chi square test. P value <0.05 was considered statistically significant.

RESULTS

A total of 51 patients were included in this study. Patients (N=26) in the stent thrombosis group were younger, more patients were having diabetes mellitus and hypertension, higher mean total cholesterol, low-density lipoprotein and lower high-density lipoprotein than the control group. Male population was predominant in both the groups. There was no statistical significant difference between the groups regarding demography. Demographic profiles of the both groups are compared in Table – 1.

Patients presented with acute stent thrombosis in 11 cases (42.30%), subacute stent thrombosis in 12 cases (46.15%), late stent thrombosis in 1 case (3.85 %) and very late stent thrombosis in 2 cases (7.69 %). After stent thrombosis,19 patients(73.00%) were managed with balloon dilatation alone, 5(19.23%) patients re-PCI with stenting (4 [15.38 %]bare metal stent & 1 [3.85 %] drug eluting stent),in 1(3.85 %) patient wire could not be crossed and 1(3.85 %) patient managed medically. All the patients in stent thrombosis group were switched from clopidogrel to prasugrel.

Table 1: Demographic profile of patients

Characteristics	Stent Thrombosis Group (N=26)	Control Group (N=25)	P value
Age, (mean ± SD, year)	56.08 ± 8.48	59.28 ± 9.16	0.194
Male, n (%)	18 (69.23 %)	20 (80 %)	0.647
Hypertension, n (%)	13 (50 %)	9 (36 %)	0.275
Diabetic, n (%)	10 (38.46 %)	9 (36 %)	0.819
Smoking, n (%)	9 (34.61 %)	12 (48 %)	0.808
ACS/recent MI, n (%)	20 (76.92%)	16 (64%)	0.505
Total Cholesterol, (mean ± SD, mg/dL)	203.69 ± 58.73	180.32 ± 39.09	0.102
LDL-C, (mean ± SD, mg/dL)	119.36 ± 30.10	112.08 ± 20.79	0.102
HDL-C, (mean ± SD, mg/dL)	33.94 ± 5.05	37.72 ± 7.96	0.128
Ejection fraction, (mean ± SD, mg/dL)	44.92 ± 0.07	49.08 ± 0.093	0.084

Table 2: Procedural characteristics

	Stent Thrombosis Group (N=26)	Control Group (N=25)	P value
Poor metabolizers, n (%)	11 (42.30 %)	1 (4.00 %)	0.021
Intermediate metabolizers, n (%)	13 (50.00 %)	14 (56.00 %)	0.847
Normal metabolizers, n (%)	2 (7.69 %)	10 (40.00 %)	0.004
Mortality, n (%)	2 (7.69 %)	0 (0.00 %)	-

Majority of the patients in both the groups had left anterior descending artery involvement. Mean stent length and number of stents per patients were numerically higher in control group than the stent thrombosis group (p value = 0.062 and 0.614, respectively). Although, the difference was not statistical significant. More than half of the population in both the groups were treated with drug eluting stents (p value = 0.0853). Further procedural characteristics are given in Table – 2.

Table 3: Genetic Analysis (CYP2C19 Allele) Assessment

	Stent Thrombosis Group (N=26)	Control Group (N=25)	P Value
LAD Involvement, n (%)	20 (76.92 %)	17 (68.00 %)	0.223
Post Dilatation, n (%)	13 (50.00 %)	9 (36.00 %)	0.102
Drug Eluting Stent, n (%)	15 (57.70 %)	14 (56.00 %)	0.853
Dissection, n (%)	3 (11.53 %)	1 (4.00 %)	0.317
GPIIb/IIIa Inhibitor, n (%)	8 (30.76 %)	6 (24.00 %)	0.593
Stent Length, (mean ± SD, mm)	23.48 ± 2.44	31.32 ± 4.81	0.062
Stents per patient, (mean ± SD, mm)	2.64 ± 0.34	2.94 ± 0.56	0.614

According to CYP2C19 allele analysis intermediate metaboliser genotype was equally prevalent in both the groups (50% stent thrombosis group vs 56% in control group, p value= 0.847), poor metaboliser genotype was more prevalent in ST group (42.30 % vs 4 % in control group, p value = 0.004) and normal metaboliser genotype was less prevalent in ST group (7.69 % vs 40% in control group, p value = 0.021)(Table – 3). Mortality was reported in 2 patients (7.69%), both belonging to the poor metaboliser genotype. First patient expired with ventricular arrhythmia on day 3 of admission and other patient expired on day 7 with progressive heart failure. Control group showed no mortality.

DISCUSSION

Stent thrombosis is a cardiac emergency which requires urgent treatment. High on treatment platelet reactivity or reduced response to clopidogrel (CYP2C19*2allele) were associated with increased risk of stent thrombosis. [8-11]

CYP2C19reducedfunction allele had significantly increased risk of cardiovascular death, myocardial infarction and stent thrombosis. [12,13] Poor clopidogrel metaboliser genotype [14] (2/2) is associated with stent thrombosis, which is further corroborated from the results of our study. In our study, mortality was seen in 2 patients both belonging to the poor metaboliser (CYP2C19 2*2*) genotype.

No difference in intermediate metaboliser genotype between the groups can be explained by the fact that, higher clopidogrel loading and maintenance dose regimens (as practised in our institute) achieves greater platelet inhibition in CYP2C19*2 carriers compared with lower dose regimens. [15]

Poor metaboliser genotype was more prevalent in patients with ST which reiterated the fact that increasing the dose of clopidogrel has minimal effect on platelet inhibition inCYP2C19 poor metabolizer. [16]

Genetic testing might help in optimising the DAPT in high risk PCI patients with increased bleeding risk. Clopidogrel dose escalation overcomes the effects of platelet inhibition inCYP2C19 intermediate metabolisers and utilisation of newer antiplatelet agents (prasugrel or ticaglerol) might be considered in poor metabolizers. [17] This study further highlights this point.

Limitations

Single centre study having shorter follow up is the major limitation of the present study.

CONCLUSIONS

This study provides some correlation between different CYP2C19genotype and stent thrombosis. Clopidogrel genetic testing might provide some help in complex/high risk PCI patients for planning doses and choice of antiplatelet treatment. Further large randomised studies with longer duration of follow-up are needed to draw any definite conclusion.

Key Message

CYP2C19genotype testing might be considered in patients undergoing complex/high risk PCI.

Conflict of interest- None

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