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 prodrug 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 CYP2C19 gene 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

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

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

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*2 allele) were associated with increased risk of stent thrombosis. [8-11]

CYP2C19 reduced function 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 in CYP2C19 poor metabolizer. [16]

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 CYP2C19 genotype 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
CYP2C19 genotype testing might be considered in patients undergoing complex/high risk PCI.

Conflict of interest - None

REFERENCES


How to cite this article: Dattatreya PV, Kumar T, Manjunath CN. CYP2C19 genotypes and stent thrombosis: is there a correlation? International Journal of Research and Review. 2020; 7(3): 218-222.