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Original article

Study of assessment of efficacy of antiplatelets in percutaneous transluminal coronary angioplasty patients

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Abstract:

Introduction: The earlier treatment plan of dual-antiplatelet therapy is based on the results of prospective, randomized large-scale clinical trials which had not include concomitant assessments of platelet function. Nowadays as per current strategy, there is observed a uniform dosing and duration of antiplatelet treatment are especially recommended irrespective of the individual patient's response to the antiplatelet therapy.

Material and methods: Present research work was carried out in department of Cardiology in Poona Hospital and Research Centre Pune. Patients who underwent PTCA with aspirin and clopidogrel in Poona Hospital and Research Centre were included in present study.

Results: In present study there was statistical significant difference between resistance to dual drug aspirin and clopidogrel resistance with baseline characteristic such as female gender, presentation like acute coronary syndrome, diabetes mellitus and tobacco users.In present study out of 280 patients we observed 15.35% patients had aspirin resistance.

Conclusion: Prevalence of dual antiplatelet resistance was higher in patients who had current use of tobacco in any form and in diabetics patients with statistical significant difference. hypertension was not statistically significant risk factor for dual antiplatelet resistance.

Keywords : dual-antiplatelet therapy , antiplatelet resistance , hypertension

Introduction:

The earlier treatment plan of dual-antiplatelet therapy is based on the results of prospective, randomized large-scale clinical trials which had not include concomitant assessments of platelet function. Nowadays as per current strategy, there is observed a uniform dosing and duration of antiplatelet treatment are especially recommended irrespective of the individual patient's response to the antiplatelet therapy. [1] The limitations of this approach have been revealed by demonstration of a wide variability in clopidogrel responsiveness in the multiple pharmacodynamic studies.[2] Aspirin and clopidogrel resistance are emerging clinical entities which have lead to severe consequences such as myocardial infarction, stroke or death. [3]

In recent years, there has been a growing acknowledgement of the association between insufficient platelet inhibitions from instituted anti platelet therapy (that is clopidogrel and or aspirin) and major adverse cardiac events (MACE). [4]Studies in PTCA patients demonstrated a significantly higher risk for post

procedure thrombotic complications in individuals that demonstrates high on-treatment platelet reactivity to Adenosine diphosphate. Hypercoagulabilty, assessed by thromboelastography (TEG) assay, has in several observational studies been associated with an increased risk of post procedural major adverse cardiac events.[5]

The prevalence of aspirin and clopidogrel resistance has been reported to be between 5 and 30% in world literature.[4] There is a great need to appropriately identify antiplatelet drug resistance so that therapy can be individualized. Hence in present research attempt is made to study resistance to antiplatelet therapy in PTCA patients.

Material and methods:

Present research work was carried out in department of Cardiology in Poona Hospital and Research Centre Pune. Patients who underwent PTCA with aspirin and clopidogrel in Poona Hospital and Research Centre Pune with following inclusion and exclusion criteria.

I. Inclusion Criteria:

1. Patients whose age ≥ 18 years.
2. Patients with indication of PTCA who took 325mg of aspirin and 600mg of clopidogrel as loading dose in acute coronary syndrome.
3. Patients with indication of PTCA who took 150mg of aspirin and 75mg of clopidogrel daily dose for at least 7 days in stable coronary artery disease (CAD).
4. Patients who were ready to give written informed consent for participation study.

II. Exclusion Criteria:

1. Known hypercoagulable states like Anti Phospholipids syndrome
2. Allergic to aspirin/clopidogrel
3. Atrial fibrillation with concomitant use of anticoagulant.
4. Serum creatinine ≥3 mg/dl
5. Pregnancy
6. Concomitant use of strong inhibitors of CYP450 3A4 and 3A5 (Clarithromycin, Erythromycin, Itraconazole, Ketaconazole)
7. Thrombocytopenia (Platelet count <1 lac/ mm^3)
8. Patients who received GP IIb/IIIa receptor inhibitors in last 7 days.

Permission was obtained from Institutional Ethics Committee (IEC) and Scientific Advisory Committee of Poona Hospital & Research Centre before initiation of the study. Patients who gave written informed consent for participation of study were enrolled.

Blood analysis was performed by Food and Drug Administration- approved Thrombelastograph Hemostasis Analyzer with Platelet- Mapping assay (Haemoscope Corp., Niles, Illinois) which relies on the measurement of thrombin-induced clot strength to enable a quantitative analysis of platelet function.

All data was tabulated and prevalence of resistance to anti platelets was noted in percentage

Results:

In all 280 subjects were enrolled in the study Patients who underwent PTCA and completed TEG test. Most of the patients were between age group of 41 – 60 years with mean age of 57.85± 10.58 years (mean ± SD). In this study 80.35% patients were male.

Majority of patients (56.79%) were presented with stable coronary artery disease (CAD).

In our study out of 280 patients, 47.5% were a diabetic, 56.8% were hypertensive and 39.6% were current users of tobacco.

Table 1 Baseline characteristic of antiplatelet resistant patients

Baseline characteristics	Aspirin resistance (n=43 patients)	Clopidogrel resistance (n=49 patients)	Dual antiplatelet Drug resistance (n =32 patients)
Mean Age Yrs(±SD)	55.83 ± 11.79	58.65 ± 11.73	58.23 ± 11.80
Male Gender	26 (60.46%)	30 (61.22%)	18 (56.25%)
ACS Presentation	30 (69.77%)	36 (73.47%)	19 (59.38%)
Diabetes Mellitus	31 (72.10%)	36 (73.47%)	23 (71.88%)
Hypertension	29 (67.44%)	34 (69.39%)	23 (71.88%)
Use of tobacco	29 (67.44%)	32 (65.31%)	21 (65.63%)
Mean Inhibition			
1 mmol AA	45%		45%
2 µmol ADP		25%	25%

Baseline characteristic of Aspirin resistant, Clopidogrel resistant and dual antiplatelet resistant patients were analyzed in table 4.

Table 2 Significance of baseline characteristic in dual antiplatelet resistant patients

Baseline characteristics	Dual antiplatelet Sensitive patients (n = 248 patients)	Dual antiplatelet Drug resistance (n =32 patients)	P value Chi- square Test
Mean Age Yrs(±SD)	57.85±10.58	58.23 ± 11.80	
Gender			p = 0.002
Male	207(83.5%)	18(56.2%)	
Female	41(16.5%)	14(43.8%)	
Presentation			p = 0.049
ACS	102(41.1%)	19(59.4%)	
Stable CAD	146(58.9%)	13(40.6%)	
Diabetes Mellitus			p = 0.003
Yes	110(44.4%)	23(71.9%)	
No	138(55.6%)	9(28.1%)	
Hypertension			p = 0.670
Yes	136(54.8%)	23(71.9%)	
No	112(45.2%)	9(28.1%)	

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Tobacco user			p = 0.001
Yes	90(36.3%)	21(65.6%)	
No	158(63.7%)	11(34.4%)	

Discussion:

In present study there was statistical significant difference between resistance to dual drug aspirin and clopidogrel resistance with baseline characteristic such as female gender, presentation like acute coronary syndrome, diabetes mellitus and tobacco users.In present study out of 280 patients we observed 15.35% patients had aspirin resistance.

In present study there was correlation between diabetes mellitus and aspirin and clopidogrel resistance with reduced sensitivity of diabetic platelets to dual antiplatelet therapy. Liu et al. [6] in study of 99 patients in China stated that fasting glucose level was independent risk factor for aspirin resistance. Ertugrul et al.[7] reported that aspirin-resistant patients, as determined by impedance platelet aggregometry, were more likely to be diabetic. Aspirin resistance was correlated positively with fasting blood glucose levels ($r = 0.224$, $P < 0.001$) and HbA1c levels ($r = 0.297$, $P < 0.0001$). Similarly, Cohen, et al. [8] stated that aspirin resistance was significantly associated with HbA1c ≥ 8% in a study of 48 diabetic patients. Furthermore, Hovens, et al.[9] revealed that suboptimal glycemic control was associated with a higher frequency of aspirin resistance in 40 diabetic patients.

Angiolillo et al. [10] reported in his study, diabetic patients had a higher number of clopidogrel nonresponders ($P = 0.04$). There is found diabetic patients have increased platelet reactivity compared to the nondiabetic subjects on combined aspirin and clopidogrel treatment.

The observed weak response to the aspirin may occur despite adequate suppression of thromboxane A2 pathway. In particular, increased cell-cell interactions (i.e., platelet-erythrocytes) and platelet exposure or reactivity to the ADP observed in diabetic patients may contribute to this phenomenon.[112] Increased platelet turnover, oxidative stress resulting in aspirin-insensitive thromboxane biosynthesis, cytosolic levels of calcium, altered in the structure of platelet membrane due to the impaired lipid metabolism, and enhanced protein glycation reducing that interaction with a drug target all affect response to the antiplatelet agents. [11]

These findings suggest better glycemic control can improve the antithrombotic effects of aspirin and clopidogrel. The present study showed that there was significant correlation between antiplatelet drug resistance and acute coronary syndrome. (p = 0.049)

Neubauer et al. in 504 patients observed that for dual antiplatelet drug resistance acute coronary syndrome ($P = 0.006$), patients with positive troponin values were strong risk factors ($p < 0.001$) [12] ACS patients are at risk of major adverse cardiovascular events due to an increased residual platelet activity in aspirin and clopidogrel treated patients as compared to those with a stable coronary artery disease.[13,14]

In present study 39% of patients were tobacco user in form of chewing and smoking. There was positive correlation between uses of tobacco and dual antiplatelet resistance. (p <0.001)

In addition, Berger et al stated that the effect of clopidogrel in reducing cardiovascular mortality was greatest among current smokers and this benefit diminished significantly in nonsmokers.[15]

Clopidogrel is a prodrug that needs to be

converted into active metabolites. Only 15% of clopidogrel will be converted into active metabolites by enzymes, including CYP1A2, 2B6, 2C9, 2C19, and 3A4/5, whereas the remaining 85% is inactivated by plasma esterase. Increased activation of the hepatic cytochrome pathway could result in increased clopidogrel response. Those variations in CYP1A2 might result in increased CYP1A2 metabolic activity in smokers and causing more inhibition by clopidogrel. [16]

Mirkel et al. showed associations of aspirin resistance with smoking (risk ratio 11.47, 95% confidence interval 6.69 to 18.63, $p < 0.0001$), including a significant interaction between smoking and aspirin resistance. [17]

Conclusion:

Prevalence of dual antiplatelet resistance was higher in patients who had current use of tobacco in any form and in diabetics patients with statistical significant difference. hypertension was not statistically significant risk factor for dual antiplatelet resistance.

Study Limitations:

1. Present study was observational study only, large data required to find out significance of antiplatelet drug resistance.
2. As there was no follow up observations included in present study hence clinical outcome of patients with antiplatelet resistance were not studied.
3. Patients who took newer antiplatelets like Prasugrel and Ticagrelor were not enrolled in study.

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