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Original Article

Oral antiplatelet therapy and platelet inhibition: An experience from a tertiary care center

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ABSTRACT

Aims and objectives: Although clopidogrel combined with aspirin is the most commonly used dual drug combination to avert thrombotic events in patients with coronary artery disease, the poor responsiveness to clopidogrel remains a concern. The objective of the current study is to assess the extent of resistance to clopidogrel, prasugrel, and ticagrelor in a real life set of patients with coronary artery disease who underwent percutaneous coronary intervention (PCI).

Materials and methods: A total of 539 patients, who underwent PCI and were on aspirin and on any of the three drugs, namely, clopidogrel, prasugrel and ticagrelor, were followed up regularly in the outpatient department. After 24 h of initiation of antiplatelet medication, response to the treatment in all the patients was assessed using thrombelastography. The average percentage platelet inhibition was assessed along with the resistance and sensitivity to the drug in each patient. Sensitivity and resistance to the specific drug was defined as >50% and <50% of mean platelet inhibition, respectively.

Results: About 99.15% of the patients treated with ticagrelor were sensitive to the drug and the difference between ticagrelor, clopidogrel, and prasugrel groups for sensitivity was significant with a p value of 0.00001, in favor of ticagrelor. It was also found that ticagrelor was significantly (p value of 0.001) associated with least resistance as compared with the other drugs assessed in the study.

Conclusions: Use of ticagrelor as dual therapy along with aspirin in patients with coronary artery disease (CAD) and undergoing PCI was associated with a significantly higher mean percentage platelet inhibition, higher sensitivity, and lower resistance as compared with the usage of clopidogrel or prasugrel.

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1. Introduction

The Million Death Study reported that cardiovascular disease (CVD) was responsible for 30% mortality in males and 25% mortality in females in India.[1] In 2008, of the >2.5 million deaths due to CVD in India, two-thirds were due to coronary heart disease (CHD) indicating the rapidly escalating burden.[2]

2. Acute coronary syndrome (ACS) and role of platelets

As the primary critical step in hemostasis, platelets are activated in the presence of an agonist in response to vessel injury. The further platelet cascade involving adhesion, activation, and aggregation is depicted in Fig. 1.[3]

2.1. *Methods for platelet function tests*[4]

The various types of platelet function tests are compared in Table 1.

Table 1 – Platelet function tests.[4]

Test	Method
Light transmission aggregometry	Used to measure low-shear, platelet-to-platelet aggregation
VerifyNow™	Fully automated Measures levels of antiplatelet therapy
Flow cytometry	Uses whole-blood samples Measures platelet glycoproteins and activation markers Uses light-emitting fluorescence to detect platelet activation
Flow cytometry using VASP assay	Monitors $P2Y_{12}$ platelet receptor inhibition
PFA-100®	Assesses high-shear platelet adhesion and aggregation

2.2. *Thromboelastography (TEG)*[5]

The TEG Platelet Mapping assay relies on evaluation of clot strength to enable a quantitative analysis of platelet function. TEG analysis provides the measure of maximum platelet function, and hence the degree of hypercoagulability and extent of inhibition needed to make the platelet therapy personalized and helps deduce the:

- Resistance to and effect of antiplatelet therapy.
- Therapeutic level of the therapy.
- Risk for ischemic or bleeding event.

2.3. *Currently available antiplatelet agents*

2.3.1. *Clopidogrel*

Clopidogrel is a pro-drug, which binds to P2Y12 receptors irreversibly, rendering the receptor unable to respond to adenosine diphosphate (ADP), thus reducing platelet function.[6] Its effect on platelet function lasts for the lifetime of the affected platelet. It has a slow onset of action and is associated with high interindividual variability with high platelet reactivity despite treatment and resistance during long-term therapy.

These factors make it difficult to predict the degree of antiplatelet response to clopidogrel. The Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis and Safety (GRAVITAS) trial evaluated the effects of increasing the dose of clopidogrel in patients with inadequate inhibition of platelet function on standard dose treatment and noted that some patients continued to have very high platelet reactivity on higher doses of clopidogrel.[7]

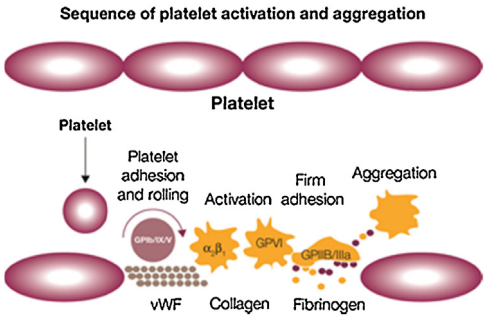

Fig. 1 – Platelet activation in response to agonist.

2.3.2. *Prasugrel*

Prasugrel is a thienopyridine and a pro-drug that needs to be converted to an active metabolite. Prasugrel attains inhibition of platelet aggregation (IPA) within 15–30 min after a loading dose of 60 mg and attains a maximum IPA of 60–70% within 2–4 h. The IPA during maintenance treatment is at an average of 50%.[7]

Prasugrel binds to the P2Y12 receptors irreversibly and produces inhibition of platelet function for the lifetime of the affected platelet. Prasugrel effects are much more predictable as revealed in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) study.[7]

Although prasugrel resistance has not been reliably described, some studies have demonstrated prasugrel resistance. Bonello et al. reported a high rate of prasugrel resistance using the vasodilator-stimulated phosphoprotein index.[8] Silvano et al. described a rare case of both clopidogrel and prasugrel resistance in a patient without diabetes, with acute STEMI due to stent thrombosis.[9] Morel et al. also observed prasugrel 'resistance' in 19% of cases with CKD.[10]

2.3.3. *Ticagrelor*

Ticagrelor is a directly acting cyclopentyltriazolo-pyrimidine (CPTP) class molecule, which does not require conversion into an active metabolite. It reversibly inhibits the P2Y12 receptors on platelets.

Ticagrelor results in an average IPA of 80–90% at 2–4 h after 180 mg loading dose. The IPAs achieved by ticagrelor were higher than the IPA typically seen with clopidogrel of around 50%.[11]

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