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# TRIPLE ANTIPLATELET THERAPY AND INCIDANCE OF DRUG RESISTANCE

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## ABSTRACT

**Background**: Evidence from small clinical studies suggests that decreased response, or 'resistance', to antiplatelet drugs is associated with subsequent major adverse clinical events. Platelet resistance is reflected as major adverse clinical events. On the basis of that we assessed the safety parameters for triple antiplatelet therapy in comparison of dual antiplatelet therapy. **Methods**: The patients who had undergone PTCA (n=120) were treated with triple (aspirin, clopidogrel and cilostazol) antiplatelet therapy or standard dual (aspirin and clopidogrel) antiplatelet therapy. Clinical safety and adverse outcomes were noted. **Results**: Results over a treatment period shows that triple antiplatelet therapy group does not increase bleeding risk compare to standard dual antiplatelet therapy group. There were 3 patients with local hematoma, 1 with sub-acute thrombosis, 2 with myocardial infarction and 2 patients with repeat intervention in triple antiplatelet therapy group. **Conclusion**: Study results show that triple antiplatelet therapy being given to prevent restenosis compared to dual antiplatelet therapy is safe to use in post-PTCA patients in real world patients in India especially in Gujarat with high doses of clopidogrel and aspirin. Because our event rates were similar we can't conclude triple antiplatelet overcome resistance in this study.

**KEYWORDS**: triple antiplatelet therapy, cilostazol, resistance.

## INTRODUCTION

Coronary artery disease is a healthcare issue of epidemic proportions and a profound impact on resource utilization. A quiescent atherosclerotic lesion may follow the course of progressive luminal encroachment, or succumb to an acute thrombotic event. Reduced de novo collagen synthesis and increased extracellular matrix metabolism contribute to weakening of the fibrous cap. Platelet aggregation is a crucial component of this process.[1] In patients with coronary artery disease (CAD) after percutaneous coronary intervention (PCI) to prevent adverse event such as acute myocardial infarction, stent thrombosis, or cardiovascular death inhibition of platelet aggregation is a major therapeutic goal for patients and healthcare providers.[2-4] Endothelial disruption and platelet recruitment, activation and aggregation are fundamental to the pathogenesis of arterial thrombosis.[5]

Percutaneous coronary intervention (PCI) with drug eluting stents (DES) is well known to reduce the re-stenosis rate to a significant extent compared to bare-metal stents (BMS) in patients with acute myocardial infarction (AMI).[6,7] It has been reported, however, that DESs increase the incidence of stent thrombosis as time passes.[8]

Cilostazol is a potent oral antiplatelet agent with a rapid onset of action that selectively inhibits phosphodiesterase III, a mechanism different from adenosine diphosphate (ADP) receptor antagonists. Previous studies have suggested that cilostazol has similar antiplatelet effects as ticlopidine or clopidogrel and similar serious adverse side effects.[9] The addition of cilostazol to aspirin and clopidogrel (triple antiplatelet therapy) has been shown to provide additional inhibition of platelet activation.[10] However, many patients are given GpIIb/IIIA inhibitors, heparin/LMWH along with triple drug therapy on top of high doses of clopidogrel up to 150 mg. and safety and tolerability of triple drug therapy has not been properly studied in these patients. We therefore studied safety and tolerability of triple antiplatelet therapy in post-PTCA patients.

There is a well documentary variability between patients (and normal volunteers) with regard to laboratory test responses to antiplatelet drugs.[11-20] Evidence from small clinical studies suggest that decreased response, or ‘resistance’, to antiplatelet drugs is associated with subsequent major adverse clinical events (MACE).[11-16,18,20-22]

Upto one third of patients exhibit normal platelet aggregation in spite of dual antiplatelet therapy with aspirin and clopidogrel. This phenomenon is often referred to as non-

responsiveness or, more commonly antiplatelet drug resistance.[23,24] The term ‘resistance’ to a drug should be used when a drug is unable to hit its pharmacological target, because of inability to reach it (as a consequence of reduced bioavailability, in vivo inactivation, or negative interaction with other substances) or to alterations of the target.[25]

## SUBJECTS AND METHODS

Study was a two-armed, open label, non-randomized, single centric and prospective trial. Subjects were treated with either double anti-platelet therapy (Aspirin 150 mg + Clopidogrel 75 mg)/BD or triple antiplatelet therapy (Aspirin 150 mg+ Clopidogrel 75 mg+ Cilostazol 100 mg)/BD.

Subjects/Patients who underwent successful PTCA during 12 month period (September 2012 to August 2013) were enrolled into study.

Patients received Cilostazol in addition to standard dual antiplatelet therapy following successful PTCA and were observed for any major adverse cardiac event. The primary endpoint was major cardiac adverse event including cardiac death, myocardial infarction, target vessel revascularization and hospitalization.

### Percutaneous coronary intervention

PTCA was done either from femoral or radial artery and a 6-7 fr sheath was inserted following catheter insertion, the procedure was performed using a guide wire. Stent/s were implanted in cases in which coronary artery stenosis was present. The type of stent was decided by the operator. Successful PCI was defined as a target vessel at the treatment site with antegrade thrombolysis in myocardial infraction-3 (TIMI-3) flow and angiographic residual stenosis less than 50% following stent implantation.

Subjects after successful PTCA who meet inclusion criteria were enrolled into study and as per investigator discretion they are enrolled into either dual antiplatelet therapy or triple antiplatelet therapy group.

No interim analyses were planned.

A safety committee was not established for this trial as it was a late phase as well as comparative trial of marketed products.

## RESULTS

Patients who meet all inclusion criteria and none of the exclusion criteria were enrolled in the study. Total 120 patients were enrolled in the study. Among these, 60 patients were allocated to the dual antiplatelet therapy (aspirin and clopidogrel) (Group 2), whereas 60 patients received triple antiplatelet therapy (Aspirin, Clopidogrel and Cilostazol) (Group 1) as a drug treatment groups. The choice of vessels treated, devices used and adjunctive medication administered to support PCI was left to the discretion of the treating physician.

After PCI, patients received either dual antiplatelet therapy (Aspirin 150 mg + Clopidogrel 150 mg) or triple antiplatelet therapy (Aspirin 150 mg+ Clopidogrel 150 mg+ Cilostazol 100 mg). Study visits were conducted at hospital discharge, at 30 days, at 90 days and 120 days.
There were no significant statistically differences between two treatment groups at study patients' entry level. Now we consider Group 1 as Triple antiplatelet therapy group and Group 2 as Dual antiplatelet therapy group.

### Safety Evaluation

During follow up period no death was observed in patient of any group. MI events were seen in both the group. Myocardial infarction occurred in 2 patients in triple antiplatelet therapy group & 1 patient in dual antiplatelet therapy group. (p=0.500). Repeat intervention needed in 2 patients in triple antiplatelet therapy group and 3 patients in dual antiplatelet therapy group (p= 0.500). Acute stent occlusions werenot observed in any group. There was no increased bleeding risk after using triple antiplatelet therapy group. Total 4 patient in triple antiplatelet therapy group and 3 patients in dual antiplatelet therapy group were observed with adverse outcome. Adverse outcome observed was shown in table 1. No mortality was noted.

In triple antiplatelet therapy group 3 patients had local hematoma, 1 patient had sub-acute thrombosis, 2 patients had myocardial infarction and 2 patients had repeat intervention. In dual antiplatelet therapy group 2 patients had local hematoma, 1 patient had sub-acute thrombosis, 1 patient had myocardial infarction, and 3 patients had repeat intervention needed. No mortality was observed in any of the group. No statistically significant difference was observed in any of these events between the two groups.

## DISCUSSION

The results of our study showed that addition of cilostazol does not significantly decrease the incidence of MACE or MACCE. Reintervention was not significantly reduced by the use of

cilostazol in addition to aspirin and clopidogrel. There was no increased bleeding in triple antiplatelet group. In our analysis, there was no significant difference between the dual and triple therapy groups in terms of bleeding risk. This result might be partially explained by a previous study showing that, cilostazol had similar effective antiplatelet action without a significant increase in bleeding time compared to clopidogrel.[26]

These study shows bleeding rate of 5% for triple antiplatelet therapy group. There were 3 patients had local hematoma, 1 patient had sub-acute thrombosis, 2 patients had myocardial infarction and 2 patients had repeat intervention was noted during the period of 24 months. This was comparable to dual antiplatelet therapy group and there is no statistically significant difference.

Sub-acute thrombosis was observed in both the groups and there was not shown statistically significant difference. Overall, there is no significant difference in bleeding rates, repeat intervention, myocardial infarction (reinfarction) and mortality in the two groups.

Therefore, cilostazol might be safely added to the conventional dual antiplatelet therapy after coronary stenting in patients with high risk for stent thrombosis.

Resistance to antiplatelet or non-responsiveness to therapy is associated with acute coronary syndrome or repeat intervention. As per results of our study total 3.33% patients from triple antiplatelet therapy group observed with myocardial infarction and 3.33% patients need repeat intervention in comparison to dual antiplatelet therapy. Because our event rates were similar we can't conclude triple antiplatelet overcome resistance in this study. But it does not confer that ischemic clinical event while on antiplatelet therapy, although reflective of treatment failure, does not necessarily indicate the resistance is present.[27]

**Table: 1 Adverse outcome observed in patients**

| Adverse outcome | Triple antiplatelet therapy group N (%) | Dual antiplatelet therapy group N (%) | P value |
|---|---|---|---|
| Retroperitoneal hematoma | 0 (0) | 0 (0) | |
| Local hematoma | 3 (5) | 2 (3.33) | 0.500 |
| Hematuria | 0 (0) | 0 (0) | |
| Sub-acute thrombosis | 1 (1.66) | 1 (1.66) | 0.500 |
| Myocardial infarction | 2 (3.33) | 1 (1.66) | 0.500 |
| Repeat intervention | 2 (3.33) | 3 (5) | 0.500 |

## CONCLUSION

Study results show that triple antiplatelet therapy being given to prevent restenosis compared to dual antiplatelet therapy is safe to use in post-PTCA patients in real world patients in India especially in Gujarat with high doses of clopidogrel and aspirin. More evidence needs to be generated for the use of the triple therapy regimen in patients undergoing PCI with BMS who have long lesions or who are diabetic. More evidence is needed for the effect of triple therapy on long-term follow up. Because our event rates were similar we can't conclude triple antiplatelet overcome resistance in this study. As well the reason for non-responsiveness to treatment is varying to patient to patients and till not fully understood due to enzyme activities; genetic polymorphism may play a role in that.

### Limitations

A few limitations need to be addressed. First, definitive statements may not be made regarding efficacy of treatment, directly to patients with a high risk of stent thrombosis, because of non-randomized nature of the prospective evaluation. Second, despite the apparently low sample size, this study was unpowered to prove meaningful differences in MACE between two groups to evaluate non-responsiveness to treatment. Third, the study was open label, making bias possible. Fourth, the reason for non-responsiveness to treatment may vary and are not fully understood.

Prospective randomized trials should be done to confirm the effects of the triple antiplatelet regimen in patients or lesions with high risk of stent thrombosis. Finally, the beneficial effects of the triple antiplatelet therapy in BMS and DES may not be differentiated. Newer antiplatelets like ticagrelor and prasugrel may be better strategy rather than triple antiplatelet therapy.

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