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Pharmacodynamic evaluation of clopidogrel reloading vs. switching to prasugrel or ticagrelor in clopidogrel resistant Indian patients

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HTPR — high on treatment platelet reactivity
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ABSTRACT

Objectives: To compare the pharmacodynamic effects of clopidogrel reloading vs. switching to prasugrel or ticagrelor in high on treatment platelet reactivity (HTPR) patients undergoing percutaneous coronary intervention (PCI).

Methods: Prospective, single-centre study wherein consecutive patients undergoing nonemergent PCI showing HTPR on 600 mg clopidogrel loading were randomized to either clopidogrel reloading (300 mg load, 75 mg OD) or prasugrel (60 mg load, 10 mg OD-in patients > 60 kg) or ticagrelor (180 mg load, 90 mg BD). HTPR is defined as maximum platelet aggregation (MPA) > 46% assessed by 5 μmol/L adenosine diphosphate light transmission aggregometry (ADP-LTA) assay after more than 6 h of clopidogrel loading. Platelet function were assessed at baseline, 6 h or more after clopidogrel loading, 2 h after reloading, day 1 and day 30 post-PCI.

Results: 107 patients enrolled in the study, 32 (29.9%) were found to have HTPR. 10 (9.3%) patients were reloaded with clopidogrel, 10 (9.3%) with prasugrel and 12 (11.2%) with ticagrelor. Mean MPA in clopidogrel, prasugrel and ticagrelor reloaded patients was 42.6 ± 12.5%, 15.8 ± 8.6% and 14.6 ± 7.2% respectively at 2 h after reloading and was 43.7 ± 13.5%, 15.4 ± 5.6% and 12.6 ± 4.6% on day 1 post-PCI. The MPA significantly reduced in prasugrel and ticagrelor cases and not in clopidogrel, also prasugrel and ticagrelor had almost similar MPA after the reload. There was no patient with continued HTPR with ticagrelor or prasugrel while 50% (5/10) of clopidogrel reloaded patients had HTPR. The pharmacodynamic efficacy of maintenance with prasugrel or ticagrelor was better than clopidogrel (MPA at day 30 post-PCI; 15 ± 9.7%, 13.9 ± 5.1% and 50.4 ± 13.1% respectively).

Conclusion: In patients undergoing PCI exhibiting HTPR after clopidogrel loading, ticagrelor or prasugrel reloading produced improved platelet inhibition which was better than clopidogrel reload and this effect was sustained during maintenance phase.

1. Introduction

Current guidelines recommend treating patients undergoing percutaneous coronary intervention (PCI) and drug-eluting stent implantation with a loading dose of P2Y12 receptor antagonist and continuation of same for at least 1 year [1]. Clopidogrel resistance has been defined as high on treatment platelet reactivity (HTPR) [2]. Variable antiplatelet responses to clopidogrel are primarily based on metabolic phenotype of cytochrome 2C19 (CYP2C19) genotype. Patients who are carriers of loss-of-function alleles in the hepatic CYP2C19 system have lower clopidogrel active metabolite levels and are thus clopidogrel resistant [3,4].

High on treatment platelet reactivity (HTPR) while on clopidogrel has been seen to be associated with high adverse event rates in patients undergoing percutaneous coronary intervention (PCI) [5–7]. Newer P2Y12 inhibitors, prasugrel and ticagrelor, are accompanied by a stronger and more consistent antiplatelet action compared with clopidogrel [8–17]. However, there is limited data on the effects of clopidogrel reloading vs. switching to prasugrel or ticagrelor in this group of HTPR patients.

In pharmacodynamic study, in post-PCI patients exhibiting HTPR, prasugrel was more effective than a double maintenance dose of clopidogrel in reducing platelet reactivity (PR) [18]. Ticagrelor therapy was associated with greater platelet inhibition compared with clopidogrel in stable CAD patients with HTPR following a 300-mg clopidogrel loading dose [19]. In the present study, we aimed to compare the pharmacodynamic effects of clopidogrel reloading vs. switching to prasugrel or ticagrelor in clopidogrel resistant Indian patients being taken up for PCI.

2. Methods

Study was a prospective randomized, single-centre, 3-arm, parallel-design study to evaluate the pharmacodynamic response of clopidogrel

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reloading vs. switching to prasugrel or ticagrelor in clopidogrel resistance patients being taken up for PCI.

2.1. Study population

Patients aged 18 to 75 years being taken for elective coronary angiography and possible revascularisation were included in the study.

Patients with acute STEMI and those undergoing urgent coronary angiography and possible revascularisation were excluded from the study. Patients were also excluded if they were already on antiplatelet therapy except aspirin and clopidogrel, had contraindications to antiplatelet therapy, were on chronic oral anticoagulation treatment, or had a history of bleeding diathesis. Patients were also excluded if there was any history of ischemic or hemorrhagic stroke, intracranial neoplasm, arteriovenous malformation or aneurysm, a history of transient ischemic attack, history of active bleeding, or were on dialysis. A written informed consent was obtained prior to the procedure in all patients as per institution protocol. Approval of the institutional ethics committee was taken for study.

2.2. Study Design

Baseline platelet function test was done before clopidogrel loading. All patients clopidogrel naive or otherwise received an initial loading dose of clopidogrel 600 mg in the night prior to the planned PCI. Platelet function was assessed after 6 or more hours of clopidogrel loading. The HTPR patients were randomly assigned in 1:1:1 ratio, using computerized random-number generation to receive 1 of the following 3 regimens: 1) clopidogrel 300 mg loading dose (LD) followed by 75 mg OD maintenance dose (MD); 2) prasugrel 60-mg loading dose (LD) followed by 10-mg OD maintenance dose (MD) in patients ≥60 kg or 3) ticagrelor 180-mg loading dose (LD) followed by 90-mg BD maintenance dose (MD). Patients with no HTPR (clopidogrel sensitive) were continued on Clopidogrel 75 mg OD. All patients received aspirin 325 mg stat followed by 150 mg/day if aspirin naive or aspirin 150 mg/day without preload if already on aspirin. Patients received an intra-arterial dose of 100 to 140 U/kg heparin at time of procedure. Use of periprocedural glycoprotein IIb/IIIa inhibitors was allowed, at the operator's discretion.

2.3. Follow-up

All patients with PCI were followed up in cardiology outpatient department at 30 days.

2.4. Assessment of platelet function

Blood samples were collected for platelet function testing before the clopidogrel LD (baseline), at 6 h or more after clopidogrel loading. Platelet function test was done using Light transmission aggregometry (LTA) assay (Chrono-log corporation, USA, Model 700 Whole Blood/Optical Lumi-Aggregometer), using doses of 5 μmol/L ADP as agonist and reported as a percentage of Maximal Platelet Aggregation (MPA).

Clopidogrel resistant patient (High on Treatment Platelet Reactivity {HTPR}) was defined as MPA >46% for a 5-μmol/L ADP-induced platelet aggregation [2]. Platelet function testing was done again 2 h after reloading with one of the three regimens in Patients with High on treatment platelet reactivity (HTPR). Platelet function testing was done in patients who had PCI on day 1 and day 30 post-PCI. Samples were processed within 1 h by operators who were blinded to treatment.

2.5. Endpoints

The primary endpoint of study was to compare efficacy of clopidogrel reloading vs. switching to prasugrel or ticagrelor in patients with High on treatment platelet reactivity (HTPR) after clopidogrel load by comparing MPA% on each of the three drug regimen at 2 h post-reload and on day 1 post-PCI. Also the efficacy of maintenance dose in the HTPR patients was compared with clopidogrel sensitive patients by comparing MPA% at end of 30 days in different study groups.

The secondary endpoint of study was a composite of major adverse cardiovascular and cerebrovascular events (MACCE) which included cardiac death, myocardial infarction, stent thrombosis; stroke and need for repeat revascularisation at time of hospital discharge and post-PCI at 30 day hospital visit. Stent thrombosis was labelled as acute, subacute, late and very late when event occurred within 24 h, 30 days, <1 year or >1 year respectively after procedure. Definite, probable and possible stent thrombosis was defined according to ARC definition [20].

Safety endpoints included bleeding complications and death from any cause at time of hospital discharge and at post-PCI 30 day

Table 1
Baseline characteristics of all groups.

	All patient	Clopidogrel sensitive	Clopidogrel reload	Prasugrel reload	Ticagrelor reload	p value
Number	107	75 (70.10%)	10 (9.30%)	10 (9.30%)	12 (11.20%)	
Age (years)	57.91 ± 8.15	57.52 ± 8.64	59.90 ± 7.85	59 ± 7.13	57.75 ± 6.32	0.81
Female	24 (22.4%)	15 (20%)	3 (30%)	2 (20%)	4 (33%)	0.697
Weight	69.22 ± 7.43	68.69 ± 8.00	68.70 ± 6.73	73.10 ± 3.54	69.75 ± 6.15	0.364
Diabetic	39 (36.4%)	27 (36%)	6 (60%)	3 (30%)	3 (25%)	0.353
Hypertensive	58 (54.2%)	43 (57.3%)	6 (60%)	5 (50%)	4 (33.3%)	0.456
Smoker	18 (16.8%)	12 (16%)	4 (40%)	1 (10%)	1 (8.3%)	0.185
Tobacco chewer	18 (16.8%)	16 (21.3%)	0 (0%)	1 (10%)	1 (8.3%)	0.255
Family history	5 (4.7%)	3 (4%)	1 (10%)	1 (10%)	0 (0%)	0.585
LDL cholesterol (mg/dl)	7.3.02 ± 25.70	75.4 ± 27.62	59.5 ± 12.55	78.80 ± 20.12	64.67 ± 21.49	0.158
HDL cholesterol (mg/dl)	31.63 ± 7.28	32.0 ± 6.76	26.40 ± 8.5	35.70 ± 7.04	30.33 ± 7.87	0.029
Total cholesterol (mg/dl)	131.42 ± 29.35	133.48 ± 30.18	115.6 ± 18.21	131.42 ± 29.35	125 ± 25.78	0.204
Triglyceride (mg/dl)	127.24 ± 54.34	122.25 ± 41.78	126.2 ± 86.83	130.6 ± 68.31	156.5 ± 74.96	0.247
CSA	54 (50.5%)	35 (46.7%)	6 (60%)	6 (60%)	6 (50%)	0.771
USA	4 (3.7%)	4 (5.3%)	0 (0%)	0 (0%)	0 (0%)	0.621
NSTEMI	10 (9.3%)	8 (10.7%)	0 (0%)	1 (10%)	1 (8.3%)	0.752
MI	36 (33.6%)	24 (32%)	4 (40%)	3 (30%)	5 (41.7%)	0.879
Old MI	21 (19.6%)	17 (22.7%)	3 (30%)	1 (10%)	0 (0%)	0.200
Prior CABG	3 (2.8%)	3 (4%)	0 (0%)	0 (0%)	0 (0%)	0.725
Prior PCI	10 (9.3%)	7 (9.3%)	1 (10%)	2 (20%)	0 (0%)	0.461
LV dysfunction	38 (35.5%)	27 (36%)	5 (50%)	3 (30%)	3 (25%)	0.651