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INCIDENCDE OF RESISTANCE OF CLOPIDOGREL AFTER CORONARY INTERVENTION IN MAYO HOSPITAL LAHORE

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Abstract:
BACKGROUND: *Dual antiplatelet therapy (APD) is the cornerstone of management of coronary artery disease in coronary interventions. The resistance pattern against clopidogrel in our influenza is unknown. The aim of this study was to evaluate the frequency of resistance / hypoactivation to Clopidogrel after percutaneous coronary intervention (PCI) in the Pakistani population.*
METHODS: *The study was conducted in the Mayo hospital, Lahore for 1 year period From June 2016 to June 2017. After informed consent, patients who underwent PCI were received 4 weeks ago. All patients received 600 mg Clopidogrel 4 to 6 hours before PCI and received 75 mg Aspirin and Clopidogrel 75 mg twice daily in addition to their routine medications. Venous blood samples were collected from all selected patients and a blocking analysis test was performed on P2Y12. The test has a "Closing Time" measured within the seconds. Patients were labeled as resistant (closing time <106 seconds), hypo-receiver (closing time between 106 and 224 seconds) and receiver (closing time> 225 seconds) based on this time. Demographic data and coronary risk factors were observed for all patients.*
Findings: *Fifty patients (38 males and 12 females) were studied. Fifteen (30%) patients responded completely to Clopidogrel-resistant, 5 (10%) hypertensive and 30 (60%) closing time criteria. None of them had a clinically significant coronary event 4 weeks after PCI.*
CONCLUSION: *More than 1/3 of the post-PCI patients are more likely to be resistant or hypoactive to clopidogrel.*
Keywords: *Clopidogrel, P2Y12 platelet antiaggregation.*

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INTRODUCTION:

Coronary angioplasty is generally important after acute coronary syndrome (ACS). Today, the standard of care requires that all patients after an ACS are prescribed a DAP (aspirin and clopidogrel) if there is no contraindication. This is necessary for antithrombotic therapy, which plays a key role in the care of ACS. The literature suggests that approximately 30% of patients are resistant to clopidogrel. At this time, we do not know that the level of platelet inhibition induced by clopidogrel will prevent atherothrombotic events. There is no definite relationship between clopidogrel and low response to thrombotic events. In these facts, the need to prescribe more potent atherothrombotic drugs such as Prasugrel, which is at an increased risk of stroke, is being debated. Clopidogrel is the most commonly prescribed antiplatelet agent for thienopyridine, but we do not have significant local data on resistance in our patients. This descriptive study was done to find clopidogrelne resistance / hypoactivation in our patients. Platelets form a monolayer upon adherence to collagen and the von Willebrand factor in the area of plaque rupture. This results in the activation and release of thromboxane A2 and adenosine diphosphate (ADP) and side agonists, and the thrombin produced by the clotting cascade activates additional thrombocytes from the work and atherothrombosis. This is why antiplatelet therapy is very important in the management of ACS and after PCI.

ANTIPLATELET AGENTS

Aspirin cyclooxygenase (COX) is irreversible: inhibits thromboxane A2 production (prothrombotic and vasoconstrictor) from the acetylation step. For reasons of ACS, stroke and peripheral short and long term management, it is also extremely useful only after PCI, at the same time, to reduce the frequency of ischemic complications after angioplasty artery disease. Unfortunately, despite the effects of aspirin, patients still have atherothrombosis. For this reason, stronger antiplatelet agents such as glycoprotein IIb / IIIa inhibitors and thienopyridines have been developed. Thienopyridines inhibit ADP irreversibly by binding to the P2Y12 receptor on the surface of platelets. This results in the inhibition of platelet activation, degradation and aggregation. Clopidogrel is an antiplatelet agent of thienopyridine. Hepatic P450 (CYP450) is a prodrug that is active in the liver to form an active metabolite . Only a small fraction of clopidogrel passes metabolism by CYP450; is often hydrolyzed by esterases with an inactive carboxylic acid derivative representing 85% of the circulating compounds associated with clopidogrel. The effect of clopidogrel is dependent on time and dose. The maximum inhibition of platelets is 50% to 60%. a daily dose of 75 mg without a loading dose gives maximum stability within 4 to 7 days while a loading dose of 300 to 600 mg provides a maximal inhibition within 4 to 24 hours. The location of clopidogrel in the cardiology registry was well established by CAPRIE and CURE studies. Furthermore, when compared with the study of Credo and compared with 75 maintenance doses, PKG with 75 mg daily dose of doxorubicin was administered for at least 6 hours before dosing with 300 mg of clopidogrel showed a daily dose of mg, a significant decrease in the events of the loading dose group found. At the same time, a PCI low-risk, clopidogrel 600 mg load is adequate and an additional benefit has been shown to be achieved by the addition of an IV inhibitor IIb / llla glycoprotein to reduce attacks after PCI early ischemia.

CLOPIDOGREL RESISTANCE

Failure of aspirin therapy has brought the issue of the possibility that some patients may be resistant to this. Evidence of aspirin resistance has been observed in patients with prior stroke. Those with aspirin resistance were more likely to have a recurrent cerebrovascular event than those who did not have resistance within 2 years. In order to describe the inability to obtain a pharmacological effect, it must be able to measure it reliably. Several studies have been performed to measure the effects of platelet function and antiplatelet agents . platelet aggregation (arachidonic acid, ADP, collagen, epinephrine, or a receptor activating peptide thrombin) is a commonly used platelet function measured by transferring platelet rich plasma light (optical aggregation) in response to an agonist. This mechanism allows different effects of the drug to be monitored by allowing agonist selection (e.g., ADP for thienopyridines). Because of inter and intrapatvic variability, responses to standardization are not significant and the results are often reported as a percentage of the reference value. Other methods include cone and plate analyzer a rapid test platelet aggregation in whole blood, under high shear. Resistance to clopidogrel is dose and time dependent and there is variability in response. The basic clinical question is "the role of an agent in the treatment of failure". In a study conducted by Gurbel et al. 96 patients undergoing coronary stenting on demand were followed at multiple time points after treatment with standard clopidogrel (75 mg daily, followed by 300 mg loading dose). (63%, 31% of patients were observed after 24 hours, 5 days at 31%, and 15% at 30 days for clopidogrel resistance experimentally defined as <10% reduction in ADP response at 5 mol /) Patients with the highest pre-treatment values were

found to have the lowest antithrombotic protection within the first 5 days. Another raporda, Muller et al. suggested that a 600 mg clopidogrel challenge, defined as a 29%, 10% reduction in response to ADP-mediated platelet aggregation, such as those after 4 hours, with a 10% for no effect is observed.
We found that / 1 ADP gave 5 mmol, 5% nonresponders and 9% semi-response and 20 µMol / L ATP, 11% nonresponders and 26% semi-response, a finding in this study (screened 105), 2 patients developed subacute thrombosis and were eligible for clopidogrel response deficit definition. Resistance to clopidogrel may be due to a variety of external and internal causes. Some of the external factors are: inadequacy or sub-dosage, drug-drug interaction, p. Omeprazole and clopidogrel, clopidogrel and atorvastatin, prodrug, lifting, absorption power variable, drug quality, adjuvant, active metabolites used and production technique pill. As for the intrinsic variability of the factors, numerical variability is the regulation of P2Y12 receptor, ADP increased release and other platelet activation pathways.

MATERIALS AND METHODS:

This descriptive study was conducted at the Cardiology Department Mayo Hospital, Lahore, Pakistan for a period of 1 Year from June 2016- June 2017. After informed consent, patients who underwent PCI were received 4 weeks ago. All patients received 600 mg Clopidogrel 4 to 6 hours before PCI and received 75 mg Aspirin and Clopidogrel 75 mg twice daily in addition to their routine medications. patients who have received irregular medication or other drugs that interfere with clopidogrel are excluded as omeprazole is excluded. Venous blood samples of all selected patients with 3.2% buffered sodium citrate were collected and venous blood samples from all patients were pooled and tested for P2Y12 blockade with PFA, 200 Siemens Innovance analysis performed, access to P2Y12 blockade with a single-use cartridge specific test clopidogrel. The test measures the "closure time" in seconds, as a possible alternative or supplement to the old bleeding time. Patients were classified, based on lock time, with hiporeactivos (time off 106-224 sec) and sensitive (time off (106 sec 225 sec)). Demographic data and coronary risk factors were observed for all patients. Statistical analysis was performed with SPSS Version 20.0. sex, smoking, diabetes, and clopidogrel resistance were reported as counts and percentages of categorical variables. Chi-square test (Fisher exact test) was performed to observe clopidogrel resistance in relation to sex. A value of P <0.05 was considered significant, and the test was administered as two tails.

RESULTS:

A total of 50 patients (38 males and 12 females) were studied. The age of the working group ranged from 38 to 70. Sixteen (32%) patients had diabetes mellitus and 11 (22%) smoked; Five (10%) patients continued to smoke after PCI. According to the value of Closing Time, 15 (30%) patients were resistant to clopidogrel, 5 (10%) were pituitary and 30 (60%) were completely recipients (Table 1).

Table-1: Demographic and Important Clinical Characteristics the Study Populations.

Characteristic		Result n(%) N=50
Gender	Male	38(76%)
	Female	12(24%)
Smoker		11(22%)
Post PCI Smoker		5(10%)
Diabetes Mellitus		16(32%)
Clopidogrel Responsiveness (Closure Time in seconds)	Non-responsive (<106)	15(30%)
	Hypo responsive (106-224)	5(10%)
	Responsive (≥ 225)	30(60%)

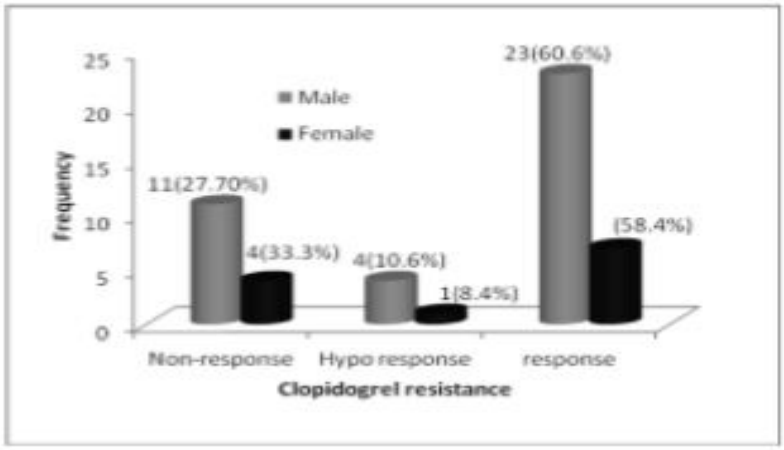
Non-diabetic men were found to have a significantly higher response rate to clopidogrel than women in the same group (Table 2).

Table-2: Association of Diabetes mellitus and clopidogrel resistance with respect to gender.

		Male N=38	Female N=12	P-value
Diabetes Mellitus	Non-responsive	4(10.52%)	2(16.67%)	0.9254
	Hypo responsive	3(7.89%)	1(8.33%)	
	Responsive	5(13.15%)	1(8.33%)	
Non Diabetes Mellitus	Non-responsive	7(18.42%)	2(16.67%)	0.0409
	Hypo responsive	1(2.63%)	2(16.67%)	
	responsive	18(47.36%)	4(33.33%)	

Nevertheless, there was no effect on the response of Clopidogrel alone (Fig. 1). Despite the high in vitro resistance to clopidogrel in any of our cases, no findings suggesting ischemia 4 weeks after PCI were reported.

Figure-1: Graphical distribution of clopidogrel resistance according to gender.



DISCUSSION:

This study has shown that the prevalence of resistance to clopidogrel in the Pakistani population is quite high. Post-PCI antiplatelet drug use is prescribed for the prevention of atherothrombosis. Only 60% of these 50 patients responded, 30% had resistance, and 10% had hypertensive patients. None of the 40% of the patients had symptoms suggestive of ischemia during the study period. Clinically, all patients were stabilized with double platelet antiaggregation (DAPT). These results show that the P2Y12 blocking assay (an in vitro evaluation) does not guide us in the clinical situation of patients. Gurbel et al. (5) evaluated platelet functions in response to ADP with optical platelet aggregation. Of the 96 patients studied, those with the highest platelet reactivities prior to treatment were at greater risk for being more reactive after 24 hours of treatment. Muller et al. also showed that 2 patients with stent thrombosis met the criteria for resistance to Clopidogrel. Soffer D et al. have shown that those who have fewer platelet inhibitors have a higher angina class after loading clopidogrel dose (450 mg). Matetzky S, et al. were associated with the absence of clinical response to clopidogrel resistance after primary angioplasty; In these patients 300 mg aspirin was given during entry to the illness and eptifibatide and heparin were given during PCI. Clopidogrel 300 mg immediately after stent implantation and 75 mg daily for 3 months. Platelet function tests were performed by stimulation with ADP (5 µmol / L) and epinephrine (10 µmol / L), followed by turbidimetric analysis with a cone and plaque analyzer (let) at the same time. Patients were divided into four of the inhibition of platelet aggregation (platelet

aggregation compared to baseline platelet aggregation).

The first quarter was those who did not respond (103 ± 8% daily compared to baseline). 69%, 58% and baseline 33% showed platelet aggregation with different levels of opposition from 2 to 4 quarters. There were eight clinical events, including stent thrombosis, myocardial infarction, recurrent ACS, and peripheral artery occlusion during quadruplicate of 1 (non-vermiyor) 7 patients (40%) who were made after 6 months. In the second quadrant (6.7%) and the cardinals had 3 or 4 recurring events in one patient in a patient. Although the study population is small, these data suggest that clopidogrel in the context of PCI after STYME may be a marker of individual variability and more generally, the risk of this resistance to clopidogrel is recurrent cardiovascular events. . Matetzky S, et al (follow-up for 6 months) reported that the rate of nonresponding events was 25% versus 40%. However, none of the responders did not have an anginal symptom. Our study had a small sample size and a short follow-up time; For this reason, we probably did not find such a finding. antithrombocide drugs have limitations, and in addition to the change in response to clopidogrel, existing evidence can not estimate the long-term future of the clinic in terms of its effectiveness. The main limitation of this study is a very short follow-up to see the small sample size and clinical events.

CONCLUSION:

It is likely that 40% of our clopidogrel-using patients, especially those on PCI, are antiplatelet agents resistant or hypoactive. However, they are not required to have ischemic symptoms or adverse cardiac events.

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