The Impact of Cigarette Smoking on Clopidogrel Induced Platelet Inhibition in Saudi Patients with Acute Coronary Syndrome Underwent Coronary Stenting

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Abstract

Purpose: The variable response to clopidogrel is multi-factorial; cigarette smoking is thought to be one of these factors as smoking is a known inducer of CYP1A2, one of the predominant isoenzymes responsible for activation of clopidogrel. The Purpose of this study is to finds out the impact of cigarette smoking on clopidogrel-induced platelet inhibition.

Methodology: retrospective analysis of a prospective cohort of 90 Saudi patients with acute coronary syndrome who underwent coronary angioplasty with drug eluting stents. Pre-procedure arterial blood sample was taken from every patient for assessment of platelet function (Verify Now P2Y12 point-of-care assay.

Results: Of these ninety patients, 26 (28.8%) patients were smokers. Patients received clopidogre l300 mg or 600mg as loading and 75mg per day as maintenance dose. The Inhibition of platelet aggregation percent (IPA %) was lower in non smokers (12.9 ± 13.1) as compared to smokers (23.8 ± 18.3) by two sample T test with p value =0.01. The mean P2Y12 reaction units (PRU) was found to be significantly higher in non smokers at 213±72 than in smokers who had mean PRU of 152 ± 66 (p>0.001). One in-hospital clinical event was encountered, with documented sub acute stent thrombosis.

Conclusion: The platelets inhibition in response to clopidogrel was lower in non smoker compared with smoker in Saudi patients who presented with acute coronary syndrome and underwent coronary stenting.

Keywords: Clopidogrel; Smoking; Platelet Function Test; Acute Coronary Syndrome

Abbreviations: DES: Drug Eluting Stent; LTA: Light Transmittance Aggregometry; PCI: Percutaneous Coronary Intervention; PRU: P2Y12 Reaction Units; IPA %: Inhibition of Platelet Aggregation Percent; ADP: Adenosine Diphosphate; PGE1: Prostaglandin E1; PAR: Protease-Activated Receptor

Introduction

Antiplatelet therapy reduces ischemic events in a wide range of patients with coronary artery disease. Efficacy of dual-antiplatelet therapy with a thienopyridine plus aspirin is well demonstrated in major randomized controlled trials of coronary stenting [1]. Clopidogrel is a prodrug, metabolized by two consecutive cytochrome P450 (CYP)-dependent steps to its active metabolite, which binds irreversibly to the platelet P2Y12 receptor. The hepatic enzymes involved in the metabolism of clopidogrel include CYP1A2, 2B6, 2C9, 2 C19, and 3A 4/5 [2]. The variability of response to clopidogrel is thought to be multi-factorial, mainly variable Genetic and environmental influences on CYP450 enzyme activity [3-6]. This great inter-patient

variability to Clopidogrel response has been shown in multiple clinical trials [7-9]. Hypo-responsiveness to clopidogrel after drug eluting stent (DES) may be detrimental to patients as is evidenced by the large-scale, prospective ADAPT-DES study [10], in which on-treatment hypo-responsiveness was an independent predictor of 1-year stent thrombosis and myocardial infarction. However, inhibitory response to clopidogrel varies considerably among individuals.

An impaired response to Clopidogrel therapy as measured by ADP-induced platelet reactivity on light transmittance aggregometry (LTA) has been associated with adverse outcomes after percutaneous coronary intervention (PCI) [11]. LTA as well as the phosphorylation assay (VASP) require special training to perform, and are not commonly used [12]. Another method to assess the effect of clopidogrel on platelet reactivity is the point-of-care test with the Verify Now P2Y12 assay (Accumetrics Inc.) [13-15].The Verify Now instrument measures platelet-induced aggregation as an increase in light transmittance and utilizes a proprietary algorithm to report values in P2Y12 reaction units (PRU).The results of this assay have been shown to be well correlated with ADP-induced platelet aggregation by LTA [12]. Recent studies have investigated Cigarette smoking and its effect on thepharmacokinetics and pharmacodynamics of clopidogrel. Cigarette smoking seems to positively modify the beneficial effect of clopidogrel [16].

Aim of the study

The aim of this study is to find out the impact of cigarette smoking on clopidogrel-induced platelet inhibition in Saudi patients presented with acute coronary syndrome and underwent coronary angioplasty with drug eluting stents.

Patients and Methods

Our study was conducted in prince Sultan cardiac center, Qassim, at central provence in Saudi Arabia. Ninety Saudi patients were enrolled including those admitted to our center from Emergency room or refered from other hospitals or health facilities. A retrospective analysis of the prospective cohort was conducted to investigate the impact of smoking on clopidogrel induced platelet inhibition. The study was approved by the ethical institutional review committee in King Fahad Specialist Hospital for which the center belongs. An informed consent was obtained from all patients prior to the study.

Patient inclusion criteria

Saudi patients were eligible for enrolment if they had acute coronary syndrome including unstable angina, non ST elevation myocardial infarction or Recent STEMI and undergone PCI with deployment of at least a single Drug Eluting Stent. Patients received a loading dose of clopidogrel300 mg or 600mg (as per preference of the primary physatain) and maintained on 75mg per day. Patients presented with Acute STEMI who underwent primary PCI were excluded. Patients with hemodynamic instability were also excluded. Patients who received glycoprotein inhibitors, heparin or thrombolysis within 24 hours before the blood sample taken were also excluded (due to potential interference with theP2Y12 assay) [17].

Methods

An arterial blood sample was collected via the procedure access (Femoral or radial artery) after the diagnostic angiography and before giving heparin for a planned PCI. The inhibitory effect of clopidogrel was measured using the Verify Now P2Y12 assay (Accumetrics Inc.) not less than 20 minutes and not more than 2 hours. The Verify Now P2Y12 assay includes 2 channels in the device. One contains adenosine diphosphate (ADP) and prostaglandin E1 (PGE1); the measurement from this channel is reported as P2Y12 reaction units (PRU). A higher PRU result reflects greater platelet reactivity mediated by P2Y12 activation. The second channel contains iso-thrombin receptor activating peptide [iso-TRAP: protease-activated receptor (PAR)-1 agonist] and PAR-4 activating peptide (PAR-4 AP). The measurement from this channel estimates maximal platelet function independent of P2Y12 receptor blockade and is reported as BASE. Inhibition of platelet aggregation (IPA %) is calculated as follows:

$$IPA\ (\%) = 100\% \times [(BASE - PRU)/BASE].$$

In our study we measured both the percent of IPA % as well as the PRU.

A. Follow up: patients were observed during hospital stay and at one month clinic visit for major cardiovascular events including death, myocardial infarction, and stroke or bleeding.

B. Statistics: Data was stored and analyzed in Mini tab 15® to generate all statistical results. Patients were divided into two groups based on their smoking history. Student's-t-test was used to spot potential differences in platelet function test and Chi-square test to find potential association. The level of significance (α) was determined to be 0.05 and a P-value of 5 percent.

C. Results: A total of 90 Saudi patients with acute coronary syndrome were included in the analysis and divided into two groups smokers (all cigarette smokers) 26 patients (28.9%) and non smokers 64 patients (69.1%).patient characteristics of the two groups were shown in (Table 1).

Table 1: Patient characteristics: Smoker versus Non smokers.

Patient Criteria	Smoker (26 patients)	Non Smoker (64patients)	P Value
Age	52years	59.18	0.022
Gender: Male	26(28.9%)	44(48.9%)	0.001
Gender: Female	0(0%)	20(22.2%)	0.001
BMI	27.45	29.52	0.078

Diabetes Mellitus	14(53.8%)	39 (60.9%)	0.77
Hypertension	10(19.2%)	39(60.9%)	0.001
Dyslipdemia	7 (26.9%)	14 (21.8%)	0.618
STEMI	15 (57.6 %)	21 (32.8%)	0.028
Non STEMI	4 (15.8%)	14 (21.8%)	0.572
Unstable Angina	7 (26.9%)	29 (45.3%)	0.086
Single vessel	13 (50%)	27 (42.1%)	0.5
Double vessel	9 (34.6%)	23 (35.9%)	0.905
Triple vessel	4 (15.4%)	8 (12.5%)	0.739

In our study, the smoker groups were all males with higher incidence of hypertension and present mostly with recent STEMI at younger age compared with non smokers. The mean time on clopidogrel (hours) was 42 ± 27 in smoker group versus 49 ± 25 in non smoker group (p <0.5). The mean Inhibition of platelet aggregation percent (IPA %) was higher in smokers (23.8 ± 18.3). as compared to non smokers (12.9 ± 13.1) with a P value<0.01. Similarly, the mean P2Y12 reaction units (PRU) was found to be significantly higher in non smokers at (213 ± 72) than in smokers who had mean PRU of (152 ± 66) with a P value <0.001 (Table2). In hospital clinical events: Only one event was observed during the one month follow up, which was a documented case of sub-acute stent thrombosis.

Table 2: Percent of platelets inhibition and PRU: Smokers versus Non Smokers.

	Smoker (26 patients)	Non Smoker (54patients)	P Value
Inhibition of platelet aggregation percent (IPA %)	23.8 ± 18.3	12.9 ± 13.1	<0.01
P2Y12 reaction units (PRU)	152±66	213±72	<0.001

Discussion

Patients with Acute coronary syndrome are expected to have a higher platelet activity and might respond to clopideogrel differently compared with stable coronary artery disease. Our study cohorts of acute coronary syndrome Saudi patients were mostly male which consists with the higher prevalence of the disease in men. Smoking is rarely reported in Saudi females. Smokers mostly present with STEMI at younger age compared with non smokers which reflect the deleterious effect of smoking resulting in coronary thrombosis. Smoking is more prevalent as sole risk factors in myocardial infarction in young. The patient's characteristics of the two groups (smokers versus non smokers) were comparable apart from the age, gender and hypertension and all has no known impact on platelet function.

Hypertension was more prevalent in nonsmoker group probably because of their higher age. In our study, we found that clopidogrel-induced Inhibition of platelet aggregation percent (IPA %) is more significant in smoker patients (23.8 ± 18.3) compared with non smokers (12.9 ± 13.1) with a P value <0.01. Likewise, the P2Y12 reaction units (PRU) of the smokers is significantly low (152±66) compared with non-smokers (213±72) with p value <0; 001. Both readings confirm the high and rapid response of smokers to clopidogrel. Our results are in consistence with several studies that report a greater platelet inhibition demonstrated in smoker patients compared with non smokers [18]. In the recent "PARADOX" trial, smoking was found to influence pharmacokinetics and pharmacodynamics of clopidogrel, in contrary toprasugrel and nonsmokers were found to have reduced responsiveness to clopidogrel compared with smokers [19].

The result of our study might be explained by Cigarette smoking is an inducer of CYP1A221, a hepatic enzyme involved in the metabolism of clopidogrel. CYP1A2 is responsible for the first oxidative step in the conversion of clopidogrel to its active metabolite. Accelerating the first step would help prevent the pro-drug from being shunted down an esterase-mediated pathway that leads to pharmacologically inactive metabolites. An alternative explanation for the association between smoking and enhanced clopidogrel effect may be the lower release of tissue plasminogen activator in current smokers [20]. Current smokers with impaired endogenous fibrinolysis may benefit most from antiplatelet therapy, an observation noted in thrombolytic therapy and coined the "smoker's paradox" [21].

However, cigarette smoking has a number of adverse effects which influence the cardiovascular system and overall health [22]. Smoking causes endothelial dysfunction and increased platelet activation leading to a prothrombotic state [23,24]. Our results do not mean that you encourage people to smoke!! Rather than highlight the lack of response in the non smoker group of patients. The clinical value of this observation still uncertain. In our cohort we encountered only one event of stent thrombosis which occurred in a non smoker.

Our study limitations include small sample size, comparison of surrogate end points rather than clinical ones. A study with large sample size with clinical end points is required.

Conclusion

Our study concludes that Clopidogrel therapy may be less effective in non smokers compared to smokers.

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