COMPARISON OF EFFECT OF LOCALLY AVAILABLE BRANDS OF CLOPIDOGREL ON PLATELET AGGREGATION IN PATIENTS WITH CORONARY ARTERY DISEASE

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Background: Anticoagulant effect of clopidogrel is of utmost importance in coronary artery disease, especially in prevention of coronary stent thrombosis. Recently, many new local brands of clopidogrel have been launched, with unknown efficacy. This study was conducted with the aim to compare two locally prepared clopidogrel brands, in terms of the effect of a loading dose of 600 mg on inhibition of platelet aggregation in patients with coronary artery disease. **Methods:** This was a double blind randomised study. Sample population consisting of 35 patients, were admitted at Lady Reading Hospital, Peshawar, for the management of coronary artery disease. Baseline platelet aggregation of all these patients was measured. These patients were divided in two groups randomly. Group-A consisting of 18 patients was given brand 'A' clopidogrel 600 mg, while Group-B consisting of 17 patients was give brand 'B' of clopidogrel 600 mg. The platelet aggregation of both groups was then measured at baseline, and at 2, 4, and 6 hours after taking the loading dose of 600 mg. **Results:** Platelet aggregation time at baseline in Group-A was 2.61±2.28 sec. and in Group-B it was 2.24±1.52 sec. (p=0.57). After 2 hours of clopidogrel administration in Group-A the platelet aggregation time was 1.44±1.58 sec. and in Group-B it was 1.53±1.107 sec. (p=0.85). Platelet aggregation time after 4 hours in Group-A was 0.28±0.57 sec. and in Group-B 1.06±1.03 sec. (p=0.009), and after 6 hours it was 0.00±0.00 sec. in Group-A and in Group-B it was 0.59±0.71 sec. (p=0.001). **Conclusion:** The two brands of clopidogrel had a significant difference in their effect on inhibition of platelet aggregation. Different brands of clopidogrel may not be equally effective.

Keywords: Platelet Aggregation, Clopidogrel, Coronary Artery Disease

INTRODUCTION

Platelet activation and aggregation play a key role in initiating and propagating coronary artery thrombosis. Inhibition of this platelet activation and aggregation by clopidogrel is of utmost importance in the treatment of coronary artery disease.[1,2] The initial haemostatic plug at sites of vascular injury is provided by the platelets. The temporary clot begins with platelet adhesion. After adhesion and recruitment of additional platelets to the site of injury, activated platelets undergo a number of changes that result in platelet aggregation, a process that allow platelets to adhere together and form a plug at the site of injury.[3–5]

The thienopyridine derivatives, ticlopidine and clopidogrel, are anti-platelet agents that inhibit platelet aggregation driven by adenosine diphosphate (ADP), thereby reducing ischemic events.[6] Several randomised trials of anti-platelet drugs show the benefit of these drugs.[7] Their purpose was to determine the extent of reduction in various subsequent risks, in particular, risks of ischemic stroke, myocardial infarction, and death from vascular disease (vascular death).[8]

Clopidogrel is an inhibitor of platelet aggregation that selectively inhibits the binding of ADP to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel remain affected for the remainder of their lifespan. Dose-dependent inhibition of platelet aggregation can be seen within 2 hours after single oral dose of Clopidogrel 75 mg. This effect on inhibition of ADP-mediated platelet aggregation reaches a steady state level between day 3 and day 7.[9,10] A number of studies have used loading dose of Clopidogrel up to 600 mg, resulting in rapid and pronounced inhibition of ADP-induced platelet aggregation inhibition.[11, 12]

Clopidogrel has been shown to effectively inhibit platelet aggregation and is at least as effective as aspirin in preventing cardiac events in patients with atherosclerosis.[13] Many studies have shown substantial reduction in the thrombotic complications particularly acute and subacute stent thrombosis with the use of clopidogrel.

Recently, many local manufacturers have launched clopidogrel at economical price. Thus, it would be pertinent to evaluate the efficacy of all these new brands.

MATERIAL AND METHODS

This study was conducted in the Cardiology Department of Postgraduate Medical Institute, Lady Reading Hospital Peshawar, from June 1, 2005 to Julyl5, 2005.

All patients, who were diagnosed as having coronary artery disease, were admitted to the cardiology unit of Lady Reading Hospital, Peshawar, and enrolled into the study. Patients with a prior event of acute coronary syndrome, hepatic insufficiency, history of significant bleeding disorder, abnormal platelet count and those already taking anti-platelet and/or anticoagulant therapy, were excluded. The patients were randomised by coin tossing method into 2 groups, i.e., 'A' or 'B'. Total number of patients was 35, 18 in Group-A and 17 in Group-B. Platelet aggregation time in both the groups was measured at base line, and after 2, 4, and 6 hours of the loading dose of 600 mg clopidogrel (Brand A) in Group-A. Platelet aggregation time was measured after 2, 4, and 6 hours after loading dose of 600 mg clopidogrel (Brand B) in Group-B. Concomitant medications needed for the treatment of underlying disease were continued.

The equipment used for platelet aggregation test was aggregometer, reagent, curettes, stir bars, micro-pipettes, isotonic saline, vacutte tubes and blood collecting adaptor. Electrical impedance aggregometry technique was employed which measures aggregation as an increase in the electrical impedance across the 2 precious metal wires resulting from the accumulation of platelets in response to an agonist. This impedance aggregation is completed in 30 minutes after a blood sample is obtained and the method provides an accurate result within 3 hours.

Blood samples were collected by direct venipuncture using vacutte tubes. After collection, the blood tubes were gently inverted several times to ensure complete mixing with sodium citrate anticoagulant present in the vacutte tube. Electrical Impedance aggregation measurements were performed on the Chronolog whole-blood aggregometer model 591. An Aliquot of whole blood (0.5 ml) was diluted with an equivalent volume of isotonic saline and incubated for 5 min at 37 ºC. The impedance of each sample was monitored at sequential 1-minute intervals until a stable baseline established. After this, the agonist ADP (20 mol/L) was then added to the sample and aggregation was measured which was monitored for 6 minutes. The final increase in ohms over this period was displayed as a numeric LED readout. In addition, a graphical print out of each electrical impedance aggregometry was also obtained. For each sample, the percent of baseline aggregation was determined by the maximum change in ohms of baseline sample. Finally, the product of the above calculation was multiplied by 100.

Data results were analysed by SPSS 10. Paired *t*-test was used to detect the difference at baseline, and at 2, 4 and 6 hours after taking 600 mg loading dose of brand 'A' and 600 mg brand 'B' clopidogrel in Group-A and Group-B respectively. Results were expressed as Mean±SD. Value of $p<0.05$ was considered significant.

RESULTS

The total number of patients was 35, 18 in Group A and 17 in Group B. Baseline characteristics of these patients are shown in Table-1. Platelet aggregation time at baseline in Group-A was 2.61±2.28 sec. and in Group-B it was 2.24±1.52 sec. (p=0.57). Platelet aggregation time after 2 hours of clopidogrel administration in Group-A was 1.44±1.58 sec. and in Group-B it was 1.53±1.107 sec. (p=0.85). Platelet aggregation time after 4 hours in Group-A was 0.28±0.57 and in Group-B it was 1.06±1.03 sec. (p=0.009). Platelet aggregation time after 6 hours of clopidogrel administration in Group-A was found to be 0.00±0.00 sec and in Group-B it was 0.59±0.71 sec. (p=0.001). Table-2.

Table-1: Baseline characteristic of the patients

Baseline Characteristics	
Total no of patients	35
No of patients completed the trial	35
Mean age (years)	51± 11 (range 30–95)
Men : Women	21: 9
Hypertension	13
Diabetes Mellitus	7
Smokers	4

Table-2: Effect of two locally available brands of clopidogrel on platelet aggregation in patients with coronary artery disease

Platelet aggregation time	Brand A 600 mg Clopidogrel	Brand B 600 mg Clopidogrel	*p*-value
0 hour	2.61±2.28	2.24±1.52	0.572
2 hours	1.44±1.58	1.53±1.107	0.854
4 hours	0.28±0.57	1.06±1.03	0.009
6 hours	0.00±0.00	0.59±0.71	0.001

DISCUSSION

The major cause of death worldwide is cardiovascular and cerebrovascular diseases which are due to atherothrombotic events, highlighting the significance of anti-platelet agents. More than 85,000 people were enrolled in previously published landmark trials such as CAPRIE[4], CLASSICS[14], CURE[15] (including PCI-CURE[16]), CREDO[17], COMMIT/CCS-2[18], and CLARITY-TIMI 28[19] studying clopidogrel alone or in combination with aspirin. These studies have enabled the international medical community to better understand the potential role of clopidogrel alone and in combination with aspirin in reducing events (myocardial infarction and stroke) caused by atherothrombotic disease. Although aspirin is the treatment of choice in atherothrombotic disease, it is given in combination with clopidogrel in patients who are post-PCI, post-CABG, or who present with MI/unstable angina/NSTEMI.

Anti-platelet therapy has immense importance particularly post-PCI and post-CABG. In most instances, outcome of intervention depends on

regular intake of prescribed drugs over a long period of time. To enhance compliance of our patients while considering their socio-economic condition, it is advisable to prefer locally manufactured quality drugs.

The present study was performed to evaluate the effect of clopidogrel from 2 different manufacturers on platelet aggregation. Drug 'A' was superior to drug 'B' in inhibition of platelet aggregation.

Although the protocol of this study was followed completely, there are some limitations. The numbers of patients were relatively small, however any bias due to inter-patient variation in values is minimised as each patient served as his own control. Platelet aggregation as measured by Electrical Impedance measurement was the surrogate end-point and not the clinical events, the results therefore do not conclusively prove the clinical efficacy of these drugs in reducing MACE. The clinical efficacy of clopidogrel has already been demonstrated and the methodology employed is standard and validated worldwide and is in routine clinical practice and research usage. The results of this study, therefore, are of definite relevance and merit a follow-up with larger clinical trials. The matter of quality of products is critical in developing countries. Our study, thus, supports the idea that the efficacy of a drug marketed in different brands, may not be the same.

CONCLUSION

The two brands of clopidogrel had a significant difference in their effect on inhibition of platelet aggregation. We conclude that different brands of clopidogrel may not be equally effective and this calls for further research before these preparations are used in patients with acute coronary syndrome, and after percutaneous coronary interventions.

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