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Original Article

Study on Clopidogrel in Inhibition of Platelet Aggregation in Suspected Angina Patients, Treated with a Daily Dose of 75 mg of Clopidogrel for 7 Days

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Abstract

This study was performed to assess the clopidogrel activity in inhibition of platelet aggregation in suspected angina patients on a daily dosag of 75 mg of clopidogrel for at least 7 days.

This clinical trial was conducted in the outpatients Department of Cardiology, Post graduate Medical Institute, Lady Reading Hospital, Peshawar from 15th October 2007 to 20th December 2007. We included 105 suspected angina patients and measured their platelet aggregation using the WBA aggregometer provided by the sponsoring pharmaceutical company. these patient were then given seven 75 mg clopidogrel tablets for one week for a once daily regimen and were asked to come for follow up after one week. Of 133 patients, 105 completed the follow up process and platelet aggregation were measured. Both readings were noted on specially designed farms prepared in accordance with the objective of the study. Patients who were on any other anti-platelet like aspirin warfarine, heparin, etc were excluded from the study.

A total of 105 patients with 28 males (52.83%) and 25 females (47.16%) were included in the study. According to age, the patients were in the range of 35 to 75 years with mean agebeing 55.79±8.74 years. Mean systolic blood pressure was 136.61±18.24 mmHg and mean diastolic blood pressure was 87.80±11.26 mmHg. Standard error of sampling for type A and type B drugs were 0.128 and 0.120, respectively. The platelet aggregation readings after follow up were zero in 73 patients (69.52%), 1-3 ohms in 26 (24.76%), and 4-6 ohms in 6 (5.71%). As a whole, clopidogrel reduced the platelet aggregation readings to below 3 ohms in 99/105 (94.28%), while in 6 (5.71%), there was some expected resistance to clopidogrel, and readings above 3 ohms were recorded. Clopidogrel has a major role in inhibition of platelet aggregation in patients with CAD. But, the activity of clopidogrel and the dose required to inhibit platelet aggregation may depend upon the individuals. Resistance to clopidogrel, especially in low doses, is expected.

Keywords: Clopidogrel; Coronary artery disease; Platelet aggregation; Peshawar.

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Introduction

In 2000, more than half of the world deaths were due to coronary artery diseases (CADs) in developing countries (1). Coronary artery diseases are the major and growing contributors to morbidity, mortality and disability in the South Asian countries including Pakistan (2). The total mortality due to cardiovascular diseases in Pakistan during 2002, estimated by WHO, were 154338 (3).

Clopidogrel is a potent oral antiplatelet agent often used the treatment of coronary artery diseases, peripheral vascular diseases, and cerebrovascular diseases. The mechanism of action of clopidogrel is irreversible blockade of the adenosine diphosphate (ADP) receptor on platelet cell membranes. This receptor is named P_2Y_{12} and is important in platelet aggregation, the cross-linking of platelets by fibrin. The blockade of this receptor inhibits platelet aggregation by blocking the glycoprotein IIb/IIIa pathway (4). Antiplatelet therapy plays a pivotal role in treatment of patients through the entire spectrum of coronary artery diseases. Platelets are believed to be integrally involved in both development and progression of the atherosclerotic heart disease, as well as in its acute thrombotic complications. While aspirin remains the traditional antiplatelet agent in patients with CAD, adverse vascular events continue to occur in patients on aspirin therapy. Clopidogrel is a relatively new antiplatelet agent and is currently one of the most widely prescribed drugs symptomatic treatment of coronary artery diseases. As a member of the class of drugs known as the thienopyridines, clopidogrel irreversibly prevents platelet activation by blocking one of the three known adenosine 5´-diphosphate (ADP) receptors on its surface (5). A study reported that clopidogrel treatment significantly reduces platelet reactivity index (PRI) only in the clopidogrel-sensitive group. The addition of clopidogrel to aspirin provides greater inhibition of platelets and can overcome aspirin resistance.the flow cytometric analysis of platelets is useful for monitoring the clopidogrel therapy (6). In clinical trials the dose of aspirin varies, but in acute coronary syndrome, clopidogrel can inhibit platelet aggregation more rapidly and more effectively at 600 mg loading dose when compared to 300 mg loading dose, while having the same degree of safety (7). Clopidogrel has superceded ticlopidine, because it is an efficacious antithrombotic drug while being less toxic than ticlopidine. However, the high inter-patient variability in response still remains an important issue. These drawbacks justify the continuing search for agents that can further improve the clinical outcome of patients with atherosclerosis through greater efficacy and/or safety (8). Furthermore, the assessment of the degree of platelet aggregation inhibition allows early (six hours after the initiation of treatment) identification of patients who are resistant to clopidogrel (9). The present study was designed to measure the inhibition of platelet aggregation byclopidogrel in suspected angina patients, treated with a daily dose of 75 mg of clopidogrel for 7 days.

Experimental

This double-blind randomized controlled trial (RCT) was conducted in the outpatients Department (OPD) of Cardiology, Post graduate Medical Institute, Lady Reading Hospita, Peshawar from 15th October 2007 to 20th December 2007. We included 133 suspected angina patients who presented with chest pain to the OPD and measured the inhibition of platelet aggregation (using the aggregometer provided by a pharmaceutical company) in these patients at the first visit. The patients were then given seven clopidogrel 75 mg tablets for one week as a once daily (OD) regimen and were asked to come for follow up after one week. They were devided into two groups: one group got a generic product and the other got the locally manufactured pidogrel. The two forms were previously labeled as A and B. Of those patients, 105 persons completed the intervention process after which 3 ml of their venous blood was taken for measuring their platelet aggregation. Both readings were written on specially designed forms prepared in accordance with the objective of the study. This study was approved by the ethical committee of Lady Reading hospital. The study was in

accordance with ICH (International Committee of Harmonization) and GCP (Good Clinical Practice) guidelines. Proper informative consent forms were signed by all the respondents.

Inclusion criteria:

1. Suspected angina patients who presented with their first ever chest pain.
2. Having ischemic changes observed in electrocardiograms (ECGs).
3. Aged between 18 to 65 years, irrespective of sex.

Exclusion criteria:

1. Established ischemic heart disease.
2. Aged more than 65 years.
3. Undergoing Coronary Artery Bypass Graft (CABG) and Percutaneous Coronary Intervention (PCI).
4. Being on any other anti-platelet drug like aspirin; warfarine, heparin, etc.
5. Bing already on clopidogrel.
6. Known hypersensitivity to clopidogrel.
7. Pregnant females and nursing mothers.

The collected data were analyzed using SPSS version 11 software, and the difference in effectiveness of both drugs in inhibition of platelet aggregation was using chi-square test and p-value. Cases with p-values less than 0.05 were was considered as significant difference.

Moreover, our trial was in accordance with CONSORT (Consolidated Standard of Reporting Trials) trial guidelines (Figure 1) (10).

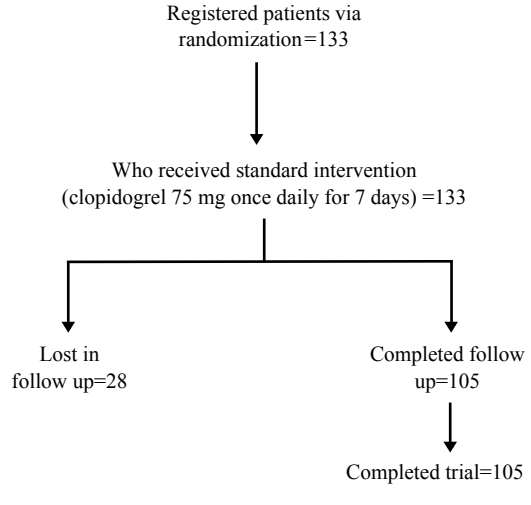

Figure 1. Flow chart of the trial loased on CONSORT trial guidelines.

Table 1. Sex distribution of patients.

Sex	Number of patients	Percentage
Males	60	57.1%
Females	45	42.9%
Total	105	100%

Results

Out of 133 patients, a total of 105 suspected angina patients consisting 60 males (57.1%) and 45 females (42.9%), who completed their follow up process, were included in the trial (Table 1). The mean systolic blood pressure (SBP) was 136.61+18.24 mmHg and the mean diastolic blood pressure (DBP) was 87.80+11.26 mmHg (Table 2).

The follow up platelet aggregation reading was 0 in 73 (69.52%), 1 to 3 ohms in 26 (24.76%), 4 to 6 ohme in 6 cases (5.71%). As a whole clopidogrel reduced the platelet aggregation readings to below 3 ohms in 99/105 (94.28%) cases while in 6 (5.72%) there were some expected resistance to clopidogrel which led to readings above 3 ohms (Table 3).

Discussion

In our study, we included the angina patients aged 35 to 65 years with a mean of 55.79+8.74 years. A World Health Organization survey has documented that the prevalence coronary heart disease in an urban population of Karachi was, more in people aged 18 to 65 years (11). In the present trial the main cause of angina in our

Table 2. Blood pressure data of patients.

Measure	Systolic BP (mmHg)	Diastolic BP (mmHg)
Mean	136.6190	87.8095
Median	140.0000	90.0000
Mode	140.00	80.00
Standard deviation	18.24638	11.26439
Range	80.00	50.00
Minimum	110.00	70.00
Maximum	190.00	120.00

Table 3. The inhibition of platelet aggregation produced by clopidogrel.

Initial reading (in ohms)	Follow up readings in (ohms) after one week							Number of patients
	.00	1.00	2.00	3.00	4.00	5.00	6.00	
2.00	1	1	-	-	-	-	-	2
3.00	2	1	-	-	-	-	-	3
4.00	3	1	1	-	-	-	-	5
5.00	3	-	-	-	-	-	-	3
6.00	3	1	-	1	-	-	-	5
7.00	8	1	-	-	-	1	-	10
8.00	9	-	1	1	1	1	-	13
9.00	14	1		-	-	-	-	15
10.00	9	3	1	-	1	-	1	15
11.00	6	1	1	2	-	-	-	10
12.00	4	-	-	2	-	-	-	6
13.00	2	-	2	-	-	-	-	4
14.00	8	-	1		-	-	-	9
15.00	1	-	-	1	-	1	-	3
16.00	-	-	1	-	-	-	-	1
17.00	-	-	1	-	-	-	-	1
Total	73	10	9	7	2	3	1	105

patients could probably be hypertension, as the mean systolic blood pressure was 136.61+18.24 mmHg and the mean diastolic blood pressure was 87.80+11.26 mmHg. In our previous study, we had observed that 43.68% of the coronary artery diseases were concomitlant with high blood pressure. In Pakistan, the average SBP of people aged 30 years and above is 130-140 mmHg (12). In this study, after the intervertion period, the platelet aggregation readings were brought to zero (0) in 73 (69.52%), 1-3 ohms in 26 (24.76%) and 4-6 ohms in cases (5.71%). As a whole, clopidogrel reduced the platelet aggregation readings to below 3 ohms (i.e. the acceptable reading) in 99/105 (94.28%). A study from Pakistan comparing a domestic brand of clopidogrel versus a generic product reported that clopidogrel is an effective antithrombotics in Pakistani population and both product were equally effective in reducing the platelet aggregation (13). Clopidogrel has been used successfully in clinical trials to prevent stroke and MI, and to prevent stent closure and graft occlusion (14). In another trial, clopidogrel was compared with aspirin in the CAPRIE (clopidogrel versus aspirin in patients at risk of ischemic events) trial. In this trial 19185 patients were randomized to receive aspirin 325 mg per day or clopidogrel 75 mg per day, for a period of 1 to 3 years. The relative risk of ischemic stroke, MI or vascular death was reduced by 8.7% in clopidogrel treated group ($p=0.043$). The results of this trial provided the evidence that clopidogrel is at least as effective as aspirin (15). The CURE (clopidogrel in unstable angina recurrent events) trial further supported the proposed hypothesis that combination of clopidogrel and aspirin is superior to aspirin alone in prevention of death, MI and stroke in patients with NSTE ACS. The results of this trial showed a significant reduction in the composite endpoint of death, MI or stroke with clopidogrel and aspirin versus taking aspirin alone (9.3% vs. 11.4%, RR 0.80, 95% CI 0.72-0.90; $p<0.001$) (16). The American College of Cardiology and American Heart Association (ACC/AHA) guidelines have also recommended the use of clopidogrel as a Class 1 indication in patients who are sensitive to aspirin or have major

gastrointestinal intolerance (17). In six cases some expected resistance to clopidogrel was recorded: readings above 3 ohms and up to 6 ohms after one week complete course of 75 mg clopidogrel a day only regimen. Recently, laboratory documentation of aspirin resistance has been shown to predict an increased risk of cardiovascular events in patients with coronary artery disease (18). A few studies have revealed important heterogeneity in platelet response to clopidogrel in patients with stable coronary artery disease (19-21), but the clinical significance of this phenomenon has not yet been investigated. In another study by Matetzky et al. (22), 25% of patients with STEMI were resistant to clopidogrel and subsequently were at increased risk of recurrent cardiovascular events in a 6-month follow-up.

Conclusion

Clopidogrel has a major role in inhibition of platelet aggregation in patients with CAD. But the ability of clopidogrel and the dose required to inhibit platelet aggregation may depend upon the individuals. Resistance to clopidogrel especially in low doses is expected.

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