RANDOMIZED DOUBLE BLIND COMPARISON OF TWO BRANDS OF CLOPIDOGREL IN INHIBITION OF PLATELET AGGREGATION

[#]Hikmatullah Jan, Muhammad Hafizullah, Asad Ali, Iram Tariq Bano, Shabana Ali, •Ali Arsalan.

[#]Department of Cardiology, Postgraduate Medical Institute, Lady Reading Hospital Peshawar, Pakistan
•Research Assistant Highnoon Laboratories Pvt.Ltd. Canada

ABSTRACT

Objectives: To compare the anti platelet effects of locally manufactured clopidogrel with the anti platelet effect of clopidogrel manufactured by multinational pharmaceutical abroad.

Methodology: A total of 118 subjects were enrolled, 18 to 65 years of age, who presented with suspected ischemic heart disease and were randomly assigned to receive either drug A (Pidogrel) or drug B (Plavix) in a double blind manner for 7 days. Platelet aggregation was measured in both the groups at baseline and at final visit.

Results: Base line platelet aggregability in both drug groups was not significantly different ($p=0.317$) Mean reduction in platelet aggregation by drug-A was 8.47+/- 0.45 ohms ($p<0.001$) and mean reduction in platelet aggregation by drug-B was 8.62+/- 0.46 ($p<0.001$). The difference in platelet aggregability at day 7(follow up) between the two groups was not statistically significant i.e., was the same.

Conclusion: Locally manufactured clopidogrel is equally effective as that manufactured by the multinational company abroad giving us the added advantage of cost effectiveness.

INTRODUCTION: Platelet activation and aggregation significantly contributes to the development of cardiovascular events. The initial step in this process is the adhesion of platelets, with the help of its receptors, to the disrupted endothelium.[1,2,3] This is followed by platelet activation, synthesis and release of different mediators including Thromboxane A_2 and ADP, which further amplify the process.[4, 5] Subsequently platelet aggregation occur which results in plug formation.[4, 6] Inhibition of this process plays important role in the prevention of cardiovascular disease.[7,8] Aspirin only partially inhibit platelet aggregation by blocking thromboxane mediated aggregation pathways.[9,10] Clopidogrel blocks P_2Y_{12} ADP receptor and thus ADP induced platelet aggregation is inhibited.[11,12] Patients having least sensitivity to the effects of aspirin on Arachidonic acid pathway were found to be highly sensitive to the ADP receptor antagonist clopidogrel.[13] Clopidogrel is now the recommended treatment in patients with acute coronary syndromes and in those undergoing PCI.[14,15] Compared with aspirin alone combination of clopidogrel and aspirin reduce the risk of ischemic events in patients undergoing PCI and non STEMI. [16, 17]

Clopidogrel is manufactured by a multinational pharmaceutical company with the brand name of Plavix. In developing countries like Pakistan, many patients with ACS or Post PCI cannot afford it for long, because of its high cost. Many local companies with different generic names have launched it. The efficacy of most of these locally manufactured clopidogrel is not known. Present study was performed to compare the anti platelet effects of locally manufactured clopidogrel with the anti platelet effect of clopidogrel manufactured by multinational pharmaceutical as measured by inhibition of platelet aggregation using whole blood aggregometry.

MATERIAL AND METHODS

This double blind randomized clinical trial was conducted in the out patients department of Cardiology, Post Graduate Medical Institute Lady Reading Hospital Peshawar, from 24th October 2007 to 28th Jan 2008. Patients aged 18-65 years, irrespective of gender, with suspected IHD presenting to cardiology OPD were included in the study. Those patients having established IHD, undergoing PCI or CABG using other antiplatelet or anticoagulant drugs, having known hypersensitivity to clopidogrel, history of bleeding disorder, or deranged RBC, WBC or platelet counts were excluded from the study. Pregnant and lactating females were also excluded. Thus a total of 118 patients were included in the study. All patients gave written informed consent to participate in the study.

Platelet aggregation study was performed with whole blood aggregometry. The machine used was Chronolog Whole Blood Aggregometer (591), which was supplied by the sponsoring company. All other instruments like cuvettes; micropipettes, saline, reagents, vacuette tube etc were also supplied by the sponsor.
On day one, 5 ml blood was drawn by direct veni puncture using vacuette tubes. After collecting the blood tubes were gently inverted several times to ensure complete mixing in the sodium citrate, anticoagulant, present in the vacuette tubes.
Patients were then randomized and given prefilled bottles containing either drug A (75mg tablets of generic Pidogrel) or drug B (75mg of branded Plavix). Patients were asked to take daily one tablet of their respective drug orally and report back on day seven.
Concomitant medications needed, were continued, with the exception of other antiplatelet and anticoagulant drugs.

From the whole blood, already drained out; 0.5 ml was diluted with an equivalent volume of isotonic saline and incubated for 5 minutes at 37^{o}C. The impedance of each sample was monitored at sequential 1-minute interval until a stable baseline was established. The agonist ADP (20 micromole/l) was then added to the sample and aggregation was monitored for 6 minutes. The aggregation results expressed as ohms (Ω) over the period was noted as pre-drug baseline reading. Graphical printout of each reading was obtained. Out of 118 patients who were enrolled in this study, 105 patients completed the follow-up on day 7 while 12 were lost to followup and 1 withdrew her consent. Each patient was asked about compliance and 5 ml of blood was again drained from each patient and the procedure repeated. To determine the anti platelet effect of the study drug, the final reading of platelet aggregation (in ohms) was recorded.
Before initiating the study, it was approved by ethical committee of Lady Reading Hospital Peshawar. This study was performed in accordance with ICH (*International Conference on Harmonisation*) and GCP (*Good Clinical Practices*) guidelines.

Statistical analysis
Data was analyzed using SPSS version 11. Paired T test was used to detect difference between the inhibition of aggregability for both drugs.

RESULTS:-A total of 105 patients with ischaemic heart disease, 60 (57.1%) males and 45 (42.9%) females. Fifty five patients (52.4%) received drug A (Pidogrel) and 50 (47.6%) patients received drug B (Plavix). Base line platelet aggregability in both drug groups was not significantly different (p=0.317).

Mean reduction in platelet aggregation by drug-A was 8.47+/- 0.45 ohms ($p<0.001$) and mean reduction in platelet aggregation by drug-B was 8.62+/- 0.46 ($p<0.001$). The difference in platelet aggregability at day 7(follow up) between the two groups was not statistically significant i.e., was the same.

DISCUSSION

Like in the western countries ischemic heart disease is also on the rise in our country. [18, 19] The beneficial effects of antiplatelet drug Clopidogrel in patients with ischemic heart disease have been investigated extensively, but majority of landmark studies were conducted in western population.[20,21] Maximum benefits of clopidogrel can be achieved when it is used regularly for a prolonged period.[14] Considering the socioeconomic status of majority of our local population, good compliance can be achieved only when low cost drugs are available. With the availability of locally manufactured clopidogrel, it is essential to test their effectiveness. In this regard very limited work has been done so far. [22, 23]

In previous studies local clopidogrel was compared with branded clopidogrel, but high loading dose of 600mg was used. The follow-up reading in these studies was taken at 24 hours or less than 24 hours duration. With high loading dose of clopidogrel, rapid onset of action can be achieved.[24]

In present study, we used low dose (75mg) of clopidogrel taken daily and follow-up reading was taken at day 7, because low dose clopidogrel has slow onset of action and reaches steady state inhibition after 4-7 days. [25] Of the currently available tests to asses the inhibition of platelet aggregation, LTA (Light Transmission Aggregometry) is considered to be the gold standard, but its use is mainly limited to specialized laboratories.[26]

In our study we used whole blood aggregometry to asses platelet aggregation inhibition because it needs short time, is reliable,[27] and is FDA approved.[28,29] WBA measures electrical impedance between two electrodes, immersed in whole blood, after addition of a platelet agonist using a chronolog aggregometer.[30,31]

In our study we compared the effects of two brands of clopidogrel in inhibiting platelet aggregation in patients with suspected CAD in our local population. Both drugs were found to have equal anti platelet effect. Our results correlate with the results of a previous local study, in which another brand of clopidogrel was used.[22] In both these studies patients with suspected ishemic heart disease were included.

On other hand another local study concluded that different brands of clopidogrel were not equally effective.[23] Unlike our study, in that study, patients with documented CAD, admitted either for ACS or undergoing PCI, were included. The disagreement in concordance between our results and the results of this study may be due to the different populations selected. It is possible that there patients were having a different haemostatic/coagulation profile and might have a higher platelet aggregability which could not be inhibited by blocking the ADP receptor with Clopidogrel.

Our study has certain limitations. It was a single centre study. Individuals selected for study were having suspected ischemic heart disease, which cannot truly represent the patients in which guidelines recommend use of clopidogrel i.e. patients with ACS and post PCI. Instead of clinical events, platelet aggregation was taken as the surrogate end point. As drugs were not taken directly in front of doctor, compliance may be another bias in the study.

Clopidogrel is an important drug used in the life threatening situations. Studies done so far in local setup include different populations, different doses and different brands of clopidogrel.

A large multicentre double blinded trial further needs to be conducted in Pakistan; simultaneously comparing efficacy of all commonly used local Clopidogrel in the same population.

CONCLUSION

In the given circumstances our findings suggest that the locally manufactured clopidogrel is equally effective as that manufactured by multinational pharmaceutical abroad giving the added advantage of cost effectiveness.

REFERENCES

1. Mendolicehie GL, Ruggeri ZM. New perspectives on Von Willebrand factor functions in hemostasis and thrombosis. Semin Hematol 2005; 42.5.
2. Berndt MC, Shen Y, Dopheide SM, et al. The vascular biology of glycoprotein I6-IX-V complex. Thromb Heamost 2001; 86: 178.
3. Furie B, Furie BC. Thrombus formation in vivo J clin Invest 2005; 115: 3355.
4. Jurk K, Kehrel BE. Platelets: Physiology and biochemistry. Semin Thromb Heamost 2005; 31: 381.
5. Yu Y, Cheng Y, Fan J, et al. Differential impact of prostaglandin H synthase I knock down on platelets and parturition. J clin invest 2005; 115: 986.
6. Easton JD. Evidence with anti platelet therapy and ADP receptor antagonist. Department of Neurology, Brown University, prvidence RI, USA Cereberovasc Dis 2003; 16(suppl) 1: 20-6.
7. Ruggeri ZM. Platelets in atherothrombosis. Nat Med 2002; 8: 1227-34.
8. CAPRIE steering committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE) Lancet 1996; 348: 1329-39.
9. Patrono C, Garcia L, Rodrignez A, et al. Lowdose aspirin for the prevention of atherothrombosis NEJM 2005; 353: 2373-83.
10. Patrono C, Coller B, Fitzgerald GA, et al. Platelet active drugs, the relation ship among does, effectiveness and side effects. The seventh ACCP conference on anti thrombotic and thrombolytic therapy. Chest 2004; 126: 234-64.
11. Roth GJ. Antplatelet therapy. In colman RW, Marder VG, Clowes AW,(eds) Hemostasis and thrombosis. 5th ed. Philadelphia, Lippincott Williams and Wilkins, 2006; 1725-1738.
12. Philips DR, Conley PB, Sinha U, Andve P. Therapeutic approaches in arterial thrombosis J thromb Heamost 2005; 3: 1577.
13. Eikelboom JW, Hankey GJ, Thom J. Enhanced antiplatelet effect of clopidogrel in patients whose platelets are least inhibited by aspirin: a randomized cross over trial. J Thromb Heamost 2005; 3: 2649-55.
14. Branwald E, Antman EM, Beasley W, et al. ACC/AHA guideline update for the management of patients with unstable angina and nonSTEM1-2002: Summary article: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on management of patients with unstable angina) Circulation 2002; 106: 1893.
15. Smith SC, Feldman TE, Hirshfeld JW. ACC/AHA SCAI 2005 guideline update for percutatnous intervention. Summary article: A report of the American College of Cardiology/American Heart Association Task force an Practical Guidelines Catheter Cardiovasc Interv 2006; 67: 87.
16. Am Heart J 2008 Jan 155(1): 93e. 1-7.
17. Steim huble SR, Berger PB, Mann JT III. Early and sustained dual antiplatete therapy following PCI. A randomized control trial JAMA 2002; 288: 2411-20.
18. American Heart Association Heart disease and stroke statistics-2004 update. Dallas, American Heart Association, 2004.

19. Samad A, Sahibzada WA, Mattu A. Incidence of acute myocardial infarction. Pak J Cardiol 1996; 7: 13-17.
20. Fox KA, Mehta SR, Peters R, et al. Benefits and risks of combination of clopidogrel and aspirin in-patient undergoing surgical revascularization for Non STEMI. The Clopidogrel in Unstable angina to Prevent Recurrent Ischemic Event (CURE) trial Circulation 2004; 110: 1202-8.
21. Scirica BM, Sabatine MS, Morrow DA, Gibson CM, Murphy SA, Wiviott SD, Guigliano RP, et al. The role of clopidogrel in early and sustained anterial patency after fibrinolysis for STEMI, the ECG CLARITY-TIMI-28 study J Am Coll Cardiol 2006; 48: 37-42.
22. Ashraf T, Ahmad M, Talpur MS, Kundi A, Faroqie AMA, Jaffery AH, et al. competency profile of locally manufactured clopidogerl complete and foreign manufactured clopidogrel plavix in patient of suspected IHD. JAMA 2005; 55(10) 443-48.
23. Bahader S, Hafizulalh M, Hasan M, Irfan M. Comparison of locally available brand of clopidogrel on platelet aggregation in patients with CAD. Abstracts: SAARC Congress of Cardiology Karachi Pakistan March 2006.
24. Savcic M, Hauert JX, Bachmann F, et al. Clopidogrel loading dose regimens: kinetic profile of pharmacodyamics response in healthy subjects. Semin Thromb Hemost 1999; 25(suppl 2): 15-19.
25. Konkel BA, Simon D, Schafer AI. Heamostasis, thrombosis, fibrinolysis and cardiovascular disease. In: Libby P, Bonow RO, Mann DL, Zipes DP, editors Braunwald's text book of cardiovascular medicine. 8th ed. Philadelphia: Saunders 2008; 2070.
26. Michelson AD. Platelet function testing in cardiovascular disease. Circulation 2004 110: e489-e493.
27. Ivandic BT, Schlick P, Staritz P, Kurz K. Determination of clopidogrel resistance by whole blood aggregometry and inhibitors of the P_2Y_{12} receptor. Clin Chem 2006; 52(3): 383-8.
28. Sweery JD, Hoerynig LA, Michnik BS. Whold blood platelet aggregation predicts in vitro and in vivo heamostatic function in the elderly. ArteriosclerThrombvasc Biol 1995; 15: 748-53.
29. Cardinal DC, Flower RJ. The electronic aggregometer: a novel device of assessing platelet behavior in blood J Pharmacol meth 1980; 3: 1350-8.
30. Burke J, Kraft WK, Grennberg. Relationship of arachidonic acid concentration to COX dependent human platelet aggregation J clin pharmacol 2003; 43: 983-989.
31. Rand ML, Leung R, Packhan MA. Platelet function assays. Transfuse Apher Sci 2003; 28: 307-317.

****