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DOES ADDITION OF CLOPIDOGREL TO ASPIRIN DECREASE PLATELET AGGREGABILITY?

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All the authors contributed significantly to the research that resulted in the submitted manuscript.

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ABSTRACT

Objectives: To compare the antiplatelet effect of aspirin alone with the antiplatelet effect of combination of aspirin and clopidogrel in cardiovascular patients.

Methodology: This study was conducted in the Jan 2008 in the out patients department of cardiology, PGMI, Lady Reading Hospital Peshawar. Patients coming to cardiology OPD and taking aspirin alone or in combination with clopidogrel for different cardiovascular diseases were included. Blood was take from each patient for measuring platelet aggregation using whole blood aggregometer and result of each individual was noted .

Results: A total of 128 patients were included. Patients who were taking only aspirin were 68. Their mean age was 52.89 ± 9.43 years. Male were 31(45.6%). Majority 46(67.6%) of these patients were suffering from ischemic heart disease (IHD). The rest were having hypertension 7(10.3%), CCF 8(11.8%), DM 3(4.4%) or PAD 4(5.9%). Patients who were taking both aspirin and clopidogrel were 60. Their mean age was 52.45 ± 8.71 years. Male were 44(73.3%). Patients were suffering from IHD 59(98.3%). Patients taking aspirin were having mean platelet aggregability of 7.10±5.89 ohms and patients taking both aspirin and clopidogrel were having mean platelet aggregability of 4.18±4.6 ohms (p=0.002). Among patients who were taking only aspirin mean aggregability of patients with IHD was7.54±5.44ohms , HTN was 10.14 ±5.87 ohms, CCF was 3.12±6.22 ohms, DM was 9.0±7.8ohms and PAD was 3.25±6.5.ohms.

Conclusion: Combination of clopidogrel and aspirin is more effective than aspirin alone in reducing platelet aggregation.

Key Words: Aspirin , Clopidogrel, Platelet aggregability

INTRODUCTION

Aspirin is the most widely used anti platelet drug world wide.[1] Its use reduces the risk of major vascular events by approximately 25% in high risk cardiovascular patients.[2] Despite aspirin use patients still suffer vascular events suggesting that aspirin does not completely inhibits platelets. This lead to the emergence of other antiplatelet drugs including clopidogrel. Aspirin and clopidogrel when given in combination acts synergistically because both drugs inhibit platelets on different pathways.[3, 4] Compared with aspirin alone combination of clopidogrel and aspirin reduce the risk of ischemic events in patients undergoing PCI and non STEMI.[5] 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.[6,7] Different aspects of clopidogrel including effect of dose and comparison of different brands have also been studied in few local studies.[8-10] We could not find any local study in which the effect of combination of clopidogrel with aspirin was studied.

Present study was performed to compare the antiplatelet effect of aspirin alone with the antiplatelet effect of combination of aspirin and clopidogrel in local cardiovascular patients.

METHODOLOGY

This study was conducted in the Jan 2008 in the out patients department of cardiology, PGMI, Lady Reading Hospital Peshawar which is the largest and oldest tertiary care hospital of the Khyber pukhtun khwa province. Patients of both Genders , aged more than 20 years and taking aspirin (75-325mg) alone or in combination with clopidogrel for at least 10 days for different cardiovascular diseases were included.

Patients taking any other anticoagulant like heparin or warfarin or having history of bleeding disorder or deranged RBS, WBC or Platelet count were excluded from the study.

The machine used for platelets aggregation was chronolog whole-blood platelet aggregometer (WBA). Other supplies needed for performing whole-blood aggregation were reagents, cuvettes, stir bars, micropipettes, tips etc.

Whole blood (0.5 ml) was diluted with an equivalent volume of isotonic saline and incubated for 5 minutes. The impedance of each sample was monitored at sequential 1-minute intervals until a stable baseline established. The agonist ADP (20 μmol/L) was then added to the sample and aggregation was monitored for 6 minutes. With time platelets aggregates over electrodes and impedance increases. The final increase in impedance (in ohms) over this period was displayed as a numeric readout. In addition, a graphical printout (i.e. chart tracing) of each electrical impedance aggregometry was also obtained. Each reading was noted on the patient's proforma.

All patients gave informed written consent to participate in the study.

Data was analyzed using SPSS version 14. Independent sample T test was used to detect difference between the aggregability of the two groups. P value of <0.05 was taken as significant.

RESULTS

A total of 128 patients were included. Patients who were taking only aspirin were 68. Their mean age was 52.89 $\pm$ 9.43 years. Patients who were taking both aspirin and clopidogrel were 60. Their mean age was 52.45 $\pm$ 8.71 years($p=0.365$). In the former group males were 31(45.6%) and female were 37(54.4%), while in the later group male were 44(73.3%) and female were 16(26.7%) {$p=0.000$}. Table 1 shows gender wise difference in age between the two groups.

Among patients taking only aspirin majority 46(67.6%) were suffering from I.H.D. The rest were having hypertension 7(10.3%), CCF 8(11.8%), DM 3(4.4%) or PAD 4(5.9%). While patients on double antiplatelets almost all (98.3%) $n=59$ were suffering from IHD.

When whole blood aggregability was performed patients taking aspirin were having mean platelet aggregability of 7.10 $\pm$ 5.89 ohms(range 0 to 21) and patients taking both aspirin and clopidogrel were having mean platelet aggregability of 4.18 $\pm$ 4.6 ohms(range 0to 17) ($P= 0.002$) (Figure 1).

Effect of gender on platelet aggregability in the two groups is shown in Table 2. In aspirin only group males had higher platelet aggregability than females, but the difference was

Table 1: Gender wise difference in age between the two groups

	Age(years)		p-value
	Male	Female	
Only aspirin	53.06 $\pm$8.94	52.75$\pm$9.95	.83
Aspirin+Clopidogrel	51.63 $\pm$9.23	54.68$\pm$6.86	.41

Table 2: Gender wise difference in platelet aggregability between the two groups

	Aggregability (ohms)		p-value
	Male	Female	
Only aspirin	7.67±6.19	6.62±5.67	.07
Aspirin+Clopidogrel	4.18±4.67	4.19±4.63	.62

Figure 1: Platelet Aggregability in patients taking aspirin alone and aspirin+clopidogrel

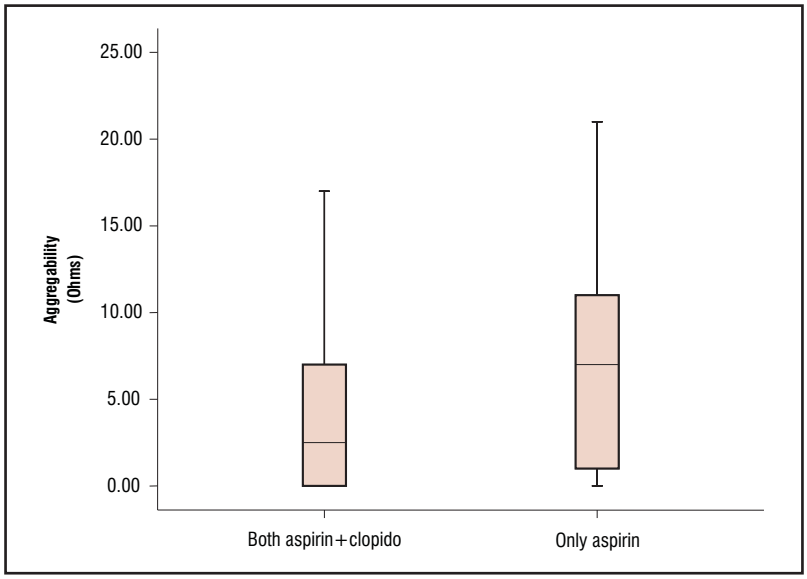


Figure 2: Platelet Aggregability in different diseases

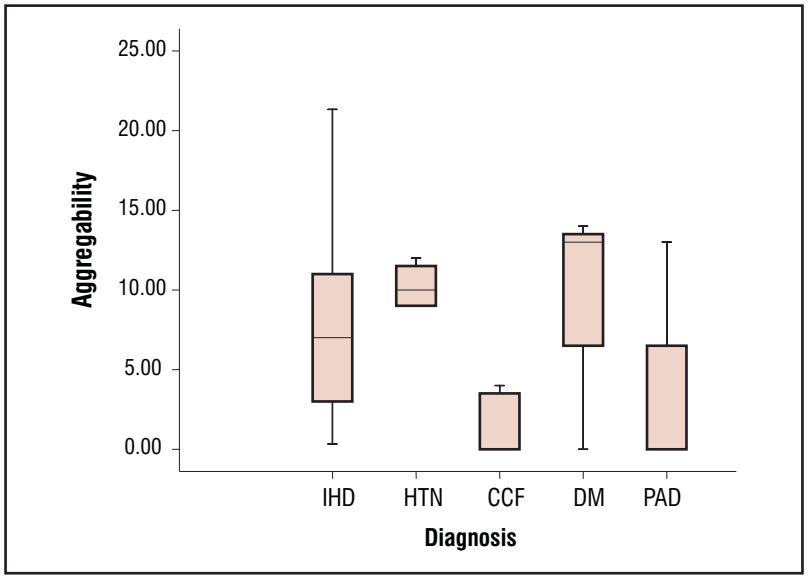


Figure 3: Correlation of age with platelet aggregability in patients taking only aspirin

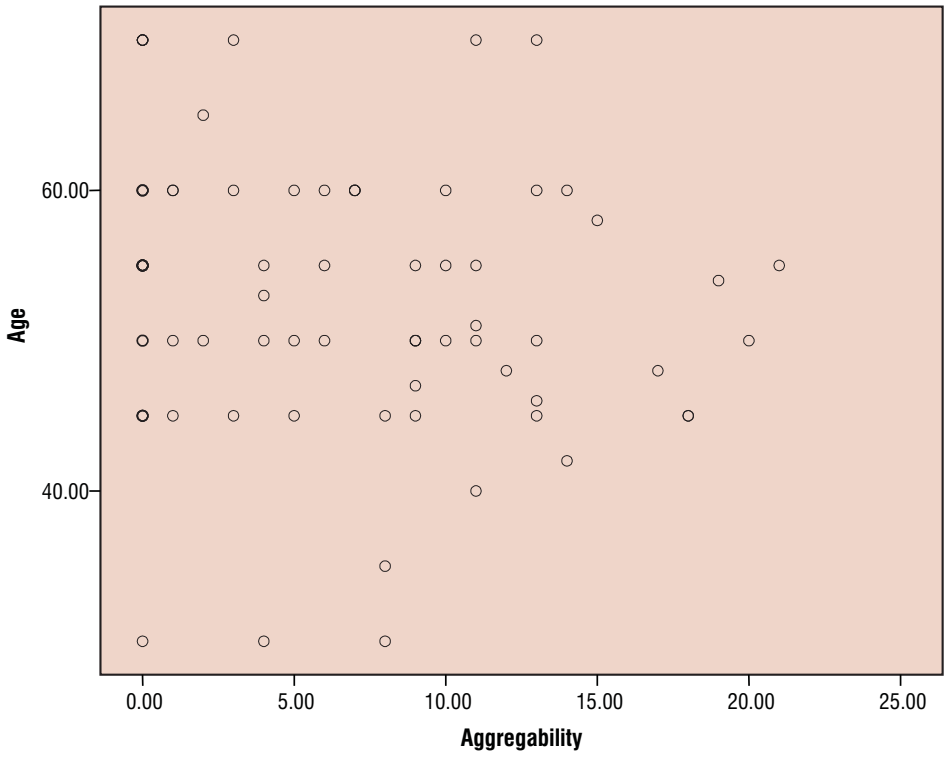
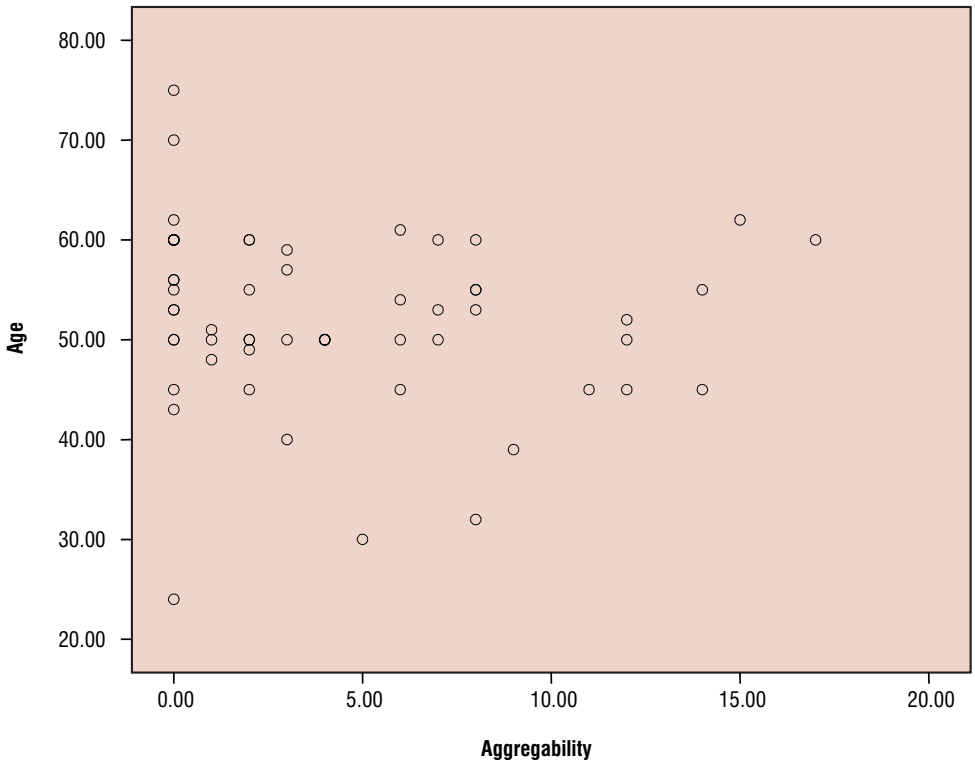


Figure 4: Correlation of age with platelet aggregability in patients taking both aspirin+clopidogrel



not statistically different. In the combination group male and female patients had almost similar platelet aggregability.

Among patients who were taking only aspirin mean aggregability of patients with IHD was7.54+_5.44 , HTN was 10.14 +_5.87, CCF was 3.12+_6.22, DM was 9.0+_7.8 and PAD was 3.25+_6.5.ohms (Figure 2).

When age was correlated with aggregability, in both groups, the correlation was found to be weakly negative and insignificant. For aspirin group pearsons correlation coefficient r=--0.177(p=0.149) and for aspirin+ clopidogrel group pearsons correlation coefficient r=--0.130(p=0.322) Figure 3 and 4.

DISCUSSION

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.[11-13] This is followed by platelet activation, synthesis and release of different mediators including Thromboxane A2 and ADP, which further amplify the process.[14,15] Subsequently platelet aggregation occur which results in plug formation[14,16] Inhibition of this process plays important role in the prevention of cardiovascular disease[17,18] Aspirin only partially inhibit platelet aggregation by blocking thromboxane mediated aggregation pathways.[19,20] Clopidogrel blocks P2Y12 ADP receptor and thus ADP induced platelet aggregation is inhibited.[3,4] 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.[21] Clopidogrel is now the recommended treatment in patients with acute coronary syndromes and in those undergoing PCI.[22,23]

The aim of present study was to find the difference between inhibition of platelet aggregation by aspirin alone and by combination of aspirin and clopidogrel. The present study proved that the combination of the antiplatelets is more effective in inhibiting platelet aggregation. These finding are in accordance with the results of other studies.[24,25]

In present study patients who were using aspirin alone, 67% were suffering from IHD, the rest were using it for other indications like CCF, DM, HTN, PAD . On the other hand almost all patients (98.3%) who were taking combination were having IHD. This points towards the guideline recommendations of use of combination of antiplatelets only in high risk patients (eg IHD) and not in other diseases. Differences between the number of male and female patients in the aspirin only group is not as high (45% vs 54%) as in the combination group (73% vs 26%).One reason for higher number of patients in combination group may be that in this group almost all patients were suffering from IHD, which is more common in men.

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]

Our study has certain limitations. It was a single centre study. Instead of clinical events, platelet aggregation was taken as the surrogate end point. Patients history about drug compliance was relied upon and blood levels of drugs was not performed.

CONCLUSION

Combination of clopidogrel and aspirin is more effective in reducing platelet aggregation.

REFERENCES

1. Jack DB. One hundred years of aspirin. Lancet 1997;350:437-9.
2. Antithrombotic Trialists Collaboration. Collaborative metaanalysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.
3. Roth GJ. Antplatelet therapy. In: Colman RW, Marder VG, Clowes AW, editors. Hemostasis and thrombosis. 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2006. p. 1725-38.
4. Philips DR, Conley PB, Sinha U, Andve P. Therapeutic approaches in arterial thrombosis. J Thromb Heamost 2005;3:1577.
5. Steim huble SR, Berger PB, Mann JT III. Early and sustained dual antiplatetet therapy following PCI. A randomized control trial. JAMA 2002;288:2411-20.
6. Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, et al. Benefits and risks of combination of clopidogrel and aspirin in patients undergoing surgical revascularization for Non STEMI. The Clopidogrel in unstable angina to prevent recurrent ischemic event (CURE) trial. Circulation 2004;110:1202-8.
7. Scirica BM, Sabatine MS, Morrow DA, Gibson CM, Murphy SA, Wiviott SD, 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.
8. Aslam N, Mehmood HR, Chaudry AH, Shamim W, Ismil

M, Awan A. Evaluation of clopidogrel in inhibition of platelet aggregation. Pak J Med Sci 2008;24:420-4.

9. 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;55:443-8.
10. Khan SB, Ullah H, Noor L, Hafeezullah M, Awan ZA, Din S . Comparison of effect of locally available brands of clopidogrel on platelet aggregation in patients with coronary artery disease. J Ayub Med Coll Abbottabad 2010;22:115-7.
11. Mendolicehie GL, Ruggeri ZM. New perspectives on Von Willebrand factor functions in hemostasis and thrombosis. Semin Hematol 2005;42:5.
12. Berndt MC, Shen Y, Dopheide SM, Gardiner EE, Andrews RK. The vascular biology of glycoprotein I6-IX-V complex. Thromb Heamost 2001;86:178.
13. Furie B, Furie BC. Thrombus formation in vivo. J Clin Invest 2005;115:3355.
14. Jurk K, Kehrel BE. Platelets: physiology and biochemistry. Semin Thromb Heamost 2005;31:381.
15. Yu Y, Cheng Y, Fan J, Chen XS, Klein-Szanto A, Fitzgerald GA, et al. Differential impact of prostaglandin H synthase I knock down on platelets and parturition. J Clin Invest 2005;115:986.
16. Easton JD. Evidence with anti platelet therapy and ADP receptor antagonist. Cereberovasc Dis 2003;16:20-6.
17. Ruggeri ZM. Platelets in atherothrombosis. Nat Med 2002;8:1227-34.
18. CAPRIE steering committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). Lancet 1996;348:1329-39.
19. Patrono C, Garcia L, Rodrignez A, Landolfi R, Baigent C. Low dose aspirin for the prevention of athero-thrombosis. N Engl J Med 2005; 353: 2373-83.
20. Patrono C, Coller B, Fitzgerald GA, Hirsh J, Roth G. Platelet active drugs, the relationship among does, effectiveness and side effects: the seventh ACCP conference on anti thrombotic and thrombolytic therapy. Chest 2004;126:234-64.
21. 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.
22. Branwald E, Antman EM, Beasley W, Califf RM, Cheitlin MD, Hochman JS, 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.
23. 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.
24. Moshfegh K, Redondo M, Julmy F, Wuillemin WA, Gebauer MU, Haeberli A, et al. Antiplatelet effects of clopidogrel compared with aspirin after myocardial infarction: enhanced inhibitory effects of combination therapy. J Am Coll Cardiol 2000;36:699-705.
25. Serebruany VL, Malinin AI, Jerome SD, Lowry DR, Morgan AW, Sane DC, et al. Effects of clopidogrel and aspirin combination versus aspirin alone on platelet aggregation and major receptor expression in patients with heart failure: the Plavix Use for Treatment Of Congestive Heart Failure (PLUTO-CHF) trial. Am Heart J 2003;146:713-20.
26. Michelson AD. Platelet function testing in cardiovascular disease. Circulation 2004;110:489-93.
27. Ivandic BT, Schlick P, Staritz P, Kurz K. Determination of clopidogrel resistance by whole blood aggregometry and inhibitors of the P2Y12 receptor. Clin Chem 2006; 52:383-8.
28. Sweery JD, Hoerynig LA, Michnik BS. Whold blood platelet aggregation predicts in vitro and in vivo heamostatic function in the elderly. Arterioscler Thrombvasc Biol 1995;15:748-53.
29. Cardinal DC, Flower RJ. The electronic aggregometer: a novel device of assessing platelet behavior in blood. J Pharmacol Methods 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;43:983-9.
31. Rand ML, Leung R, Packhan MA. Platelet function assays. Transfus Apher Sci 2003;28:307-17.