REPORT

FREQUENCY OF ASPIRIN RESISTANCE IN PATIENTS WITH CORONORY ARTERY DISEASE IN PAKISTAN

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ABSTRACT

Aspirin resistance is an emerging clinical entity. However the data available on aspirin resistance in Asian population is scarce. This study was initiated to prospectively evaluate the frequency of aspirin resistance in patients with stable coronary artery disease (CAD) in Pakistan. A cross sectional prospective study was conducted in cardiology and hematology departments at Shifa International Hospital, Islamabad from January to December 2007. Two hundred and fifty patients were enrolled from cardiology out patient department having met the specific inclusion criteria. Details were entered on a pre-designed questionnaire and aspirin response assay was performed on IMPACT–R (Dia Med AG 1785 Cressier Morat, Switzerland). Data was analyzed using SPSS V12. Aspirin resistance was observed in 12% of patients. 73.2% of study population were male and 26.8% were female, with a mean age of 57.2 years. There was no significant correlation of aspirin resistance with traditional risk factors like Diabetes Mellitus (DM), Hypertension or Dyslipidemia. 84% of Aspirin non responders were taking 75mg per day and 16% were on 150mg per day. A positive trend was noted between aspirin resistance and cigarette smoking. Aspirin resistance is a real phenomenon in Pakistani population with an estimated frequency of 12%. Large scale prospective randomized trials with long term follow up are needed to assess the impact of different doses and the clinical significance of this biochemical entity.

Keywords: Aspirin resistance, Aspirin response assay, coronory artery disease.

INTRODUCTION

Acetylsalicylic acid was first developed commercially about 110 years ago in 1897 by Felix Hoffman and was registered under the name Aspirin (Jack 1997). Clinical trials have shown the efficacy of aspirin in both primary and secondary prevention of myocardial infarction, stroke and cardiovascular. The Antiplatelet Trialists Collaboration has shown a 25% reduction in stroke, myocardial infarction (MI) or cardiovascular death with the use of aspirin (Antiplatelet Trialist collaboration 1994, 2002). However, aspirin has been shown to have variable antiplatelet activity in individual patients. Studies have demonstrated that 5-45% of patients do not achieve an adequate antiplatelet effect with aspirin (Gum 2001, Helgason 1993, Pappas 1994, Rotameter 1991, Valles 1998). Clinically, aspirin resistance refers to patients who have ischemic event despite taking this drug (Helgason 1994, Vegar 1990). Biochemically, aspirin resistance refers to patients who are taking aspirin but do not display an adequate degree of platelet inhibition No published data exists on aspirin resistance in Pakistan. The present study was undertaken in view of epidemic proportion of coronory artery disease in Pakistan (Jafer, 2005).

PATIENTS AND METHODS

Study design

This was a cross sectional study conducted at the department of cardiology and hematology at Shifa International Hospital (SIH) from July 2006 to July 2007. SIH is an academic tertiary care hospital providing medical care to racially and economically diverse population covering the Northern Pakistan. A total of 250 patients with established cardiovascular disease and/or coronory artery disease equivalent conditions, attending cardiology out patient department and meeting the inclusion criteria were included.

Inclusion criteria

* Established coronary artery disease for at least 2 months (documented history of MI, and/or past history of percutaneous coronory intervention (more than 1 year ago) and /or coronory artery bypass graft surgery(CABG)
* Coronary artery disease equivalent conditions (DM, carotid artery disease, peripheral vascular disease)
* Age more than 21 years,
* On aspirin (75-300mg/day) for more than seven days (no other anti platelet therapy)

Exclusion criteria

- Administration of ticlopidine, dipyridamole, clopidogrel or other NSAID
- Administration of heparin or enoxaparin in last 24 hours
- Family or personal history of bleeding disorders
- Platelet count less than 150,000 or more than 450,000

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- Hemoglobin less than 8mg/dl
- History of myeloproliferative disorder
- Major surgical procedure in last one week

The study protocol was reviewed and approved by the Shifa College of Medicine and Shifa International Hospital ethical and institutional review board. Informed consent was obtained from all patients enrolled in the study.

Sample size

The WHO statistical software was used to calculate an adequate sample size required for the study. Estimated frequency of aspirin resistance in general population is around 5-45% (Gum 2001, Helgason 1993, Pappas 1994, Rotameter 1991, Valles 1998). With a projected frequency of aspirin resistance at 20% in our population the sample size for 95% confidence interval was estimated to be 242. For contingencies such as incomplete data, losses to follow up, the sample size was inflated to 250.

Aspirin assay

The lab staff was blinded to the demographic details of the patients. 3ml of venous blood was taken in the blue capped bottle having sodium citrate as anticoagulant. Aspirin response assay was performed on IMPACT–R (Dia Med AG 1785 Cressier Morat, Switzerland), a fully automated aspirin response assay within three hours of sample collection. IMPACT–R takes 130 micromoles of whole blood after incubation with arachidonic acid, as sample. Platelet adhesion and aggregation on the polystyrene surface is evaluated using an image analysis system. The results were expressed as the percentage of surface covered (%SC) by platelet aggregates on polystyrene wall and average particle size (AS um2) Data collected was fed in SPSS version 12. A p value of 0.05 was considered significant.

RESULTS

The mean age of study population was 57.2 years. Out of them 73.2% were males and 26.8% were females. Table 1 shows the general characteristics of study population. Aspirin resistance was observed in 12% of the patients (fig. 1). Out of the aspirin resistant population 25 (84%) were taking 75mg of aspirin and 4 (16%) were taking 150mg (fig. 2). There was no significant correlation of aspirin resistance with risk factors like DM, Hypertension or dyslipidemia. However there was a slight trend towards relationship of aspirin resistance with smoking (p value 0.07). 78.8% of patients were taking 75mg of aspirin, 17.2% were taking 150mg of aspirin and only 4% were taking 300mg of aspirin.

Table 1: General characteristics of the study population

Variable	Mean ± SD	Range
Age (Years)	57.4±10.4	30-96
	Frequency	Percentage
Gender		
Male	183	73.2
Female	67	26.8
HTN		
Yes	103	41.2
No	147	58.8
Smoking		
Yes	14	5.6
No	236	94.4
DM		
Yes	127	50.8
No	123	49.2
Dyslipidemia		
Yes	85	34
No	165	66
Previous MI		
Yes	43	17.2
No	207	82.8
Family history of CAD		
Yes	24	9.6
No	226	90.4
History of CABG		
Yes	73	29.2
No	177	70.8
History of PCI		
Yes	49	19.6
No	201	80.4
Carotid disease		
Yes	9	3.6
No	241	96.4
Positive stress scan/ETT		
Yes	16	6.4
No	234	93.6
Dose of aspirin (mg)		
75	192	79.2
150	42	16.8
300	10	4.

DISCUSSION

Aspirin is effective for both the primary and secondary prevention of atherothrombotic events and there is robust data in favor of this evidence (Antiplatelet Trialist collaboration 1994, 2002, Gum 2001). However recently concern has been raised regarding patients who are resistant to the beneficial effects of aspirin. A recent review article puts the prevalence of aspirin resistance

between 5.5 and 60% of patients using aspirin depending upon the definition used and parameters measured (Armen 2008). Moreover this review emphasizes that complex interactions between age, gender and ethnicity need to be considered while investigating aspirin resistance. To date only a limited number of clinical studies are available in this regard, especially from South-East Asian region. A study conducted by an Indian hospital prospectively evaluated 50 stable patients of CAD and revealed that Aspirin resistant was observed in 2.8% of patients, whereas 39.58% were Aspirin semi responders (PA Sadiq 2005). The study population in this survey were ethnically and racially closer to our study population. Our study, which to our knowledge is the largest from this part of the world, reveals that a substantial number (12%) of patients on long term aspirin show biochemical evidence of aspirin resistance.

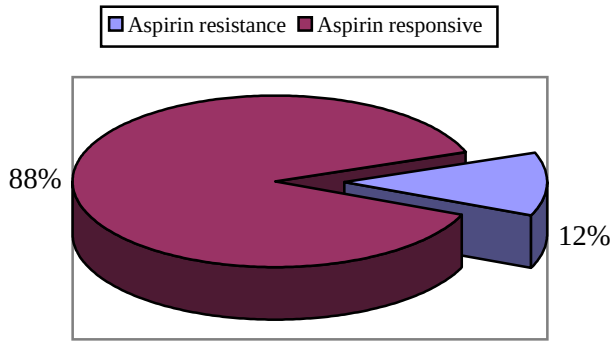

Fig. 1: Aspirin responsiveness versus aspirin resistance

There are a number of modifiable and non modifiable factors that can influence aspirin's ability to inactivate platelets and there is data supporting the conjecture that cigarette smoking may accentuate platelet thrombosis where by causing platelet hyperactivity (Coma 2004). A similar study conducted by Hung (1995) showed that smoking was significantly associated with aspirin resistance and was more in men using tobacco. Our study also revealed a trend suggesting relationship between aspirin resistance and smoking (p value 0.07%).

Studies have also suggested that higher mean concentration of LDL and total cholesterol are associated with aspirin resistance (Friend 2003). However our study did not show any significant relationship of aspirin resistance with high LDL levels, (>100mg/dl) mainly because most of our patients were taking statins. We also did not find any significant correlation between aspirin resistance and diabetes or hypertension.

An important finding in our study is a dose dependent aspirin response, which has significant practical implications. Amongst the 12% aspirin resistant population, 84% were taking 75mg of aspirin where as 16% were taking 150mg of aspirin. Hence aspirin resistance was significantly higher in individuals who were on low doses of aspirin. The clinical significance of this observation is not clear at this time. Low dose aspirin is commonly used for the secondary prevention of cardiovascular and cerebrovascular events, and though randomized trials have revealed similar safety profile of low and high dose aspirin (Hennekens 2006), nonetheless, dosing considerations should include evaluation of a patient's individual clinical status and overall cardiovascular risk. The latest AHA/ACC guidelines for secondary prevention for patients with coronory and other atherosclerotic disease 2006 update, recommend a dose ranging from 75-325mg for secondary prevention of coronory artery disease. While some studies have suggested that higher doses may yield additional cardiovascular benefits (Kong 2004), despite numerous clinical trials, the appropriate dose of aspirin to prevent major adverse cardiac events is still controversial. Since platelets can be activated by pathways other than those blocked by aspirin, better understanding of aspirin-resistant population will facilitate identification of patients who require higher aspirin doses or alternative forms of antiplatelet therapy (Armen 2008). Our study highlights the importance of this fact.

Our study focussed on the biochemical resistance to aspirin which was due to lack of a standard definition of aspirin resistance. Only a few well designed prospective studies have been conducted which term "biochemical or laboratory" and "clinical" aspirin resistance in combination (Armen 2008). Unfortunately these studies also lack a standardized definition of aspirin resistance because of variability of the assays used. There is an urgent need to define aspirin resistance comprehensively, keeping in mind both biochemical and clinical implications of aspirin resistance. Some researchers argue that aspirin resistance may not be absolute over time and measurement of aspirin resistance should be done more than once as a single measure may overestimate its prevalence (Angiololli 2005). We intend to study aspirin resistant individuals separately with one year follow up, including the effect of increasing the dose to 150mg per day. Our study presents the frequency of aspirin resistance, but because the sample size represents a diverse community and our hospital is a tertiary care facility, therefore the frequency of aspirin resistance can be surrogated as prevalence in the community.

Limitations

Our study was a cross sectional study with its inherent limitations. The exact prevalence may be different from the observed frequency. The clinical significance of the observed aspirin resistance in this population remains to be studied.

CONCLUSION

This study shows that Aspirin resistance might be a real phenomenon in Pakistan with an estimated frequency of 12% particularly in those using low dose aspirin. Larger prospective randomized trials with long term follow up are needed to assess the clinical significance of this emerging biochemical entity and the impact of low dose versus high dose of aspirin.

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REFERENCES

AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease (2006). Update. *Circulation,* **113**: 2363-2372.

Angiololli DJ, Bernardo E, Ramirez C, Ortiz AF, Sabate M, Quevedo PJ (2005). Assessment of individual response to aspirin over time: is aspirin resistance a sustained phenomenon? *J. Am. Coll. Cardiol.,* **45**: 387A.

Antiplatelet Trialist Collaboration (1994). Collaborative overview of randomized trial of antiplatelet therapy. Prevention of death, myocardial infarction and stroke in prolonged antiplatelet therapy in various categories of patients. *BMJ,* **308**: 81-106.

Antithrombotic Trialist Collaboration (2002). Collaborative Meta analysis of randomized trials of anti platelet therapy for prevention of death, myocardial infarction and stroke in prolonged antiplatelet therapy in various categories of patients. *BMJ,* **324**: 74-86.

Armen YG, Timothy W and Gregory YH (2008). The role of aspirin in cardiovascular prevention: implications of aspirin resistance. *J. Am. Coll. Cardiol*., **51**: 1829-1843.

Coma-Canella I, Velasco A, Martin A and Nasarre E (2004). Aspirin resistance is related to ischemic heart disease, male gender and tobacco. *Eur. Heart J.*, **25**: 90-91.

Friend M, Vucenik I and Miller M (2003). Platelet responsiveness to aspirin in patients with hyper-lipidaemia. *BMJ,* **326**: 82-83.

Gum PA, Kottke-Marchant K, Poggio ED, Gurm H, Welsh PA, Brooks L, Saap SK, Topol EJ (2001). Profile and prevalence of aspirin resistance in patients with cardiovascular disease. *Am. J. Cardiol.,* **88**: 230-235.

Helgason CM, Bolin KM, Hoff JA, Winkler SR, Mangat A, Tortorice KL and Brace LD (1994). Development of aspirin resistance in persons with previous ischemic stroke. *Stroke,* **25**: 2331-2336.

Helgason CM, Tortorice KL, Winkler SR Penney DW, Schuler JJ, McClelland TJ and Brace LD. (1993). Aspirin response and failure in cerebral infarction, *Stroke*, **24**: 345-350.

Hennekens CH, Sechenova O, Hollar D and Serebruany VL (2006). Dose of aspirin in the treatment and prevention of cardiovascular disease: Current and future directions. *J. Cardiovasc. Pharmacol. Ther.*, **11**(3): 170-176.

Hung J, Lam JY, Lacoste L and Letchacovski G (1995). Cigarette smoking acutely increases platelet formation in patients with coronary artery disease taking aspirin. *Circulation,* **92**: 2432-2436.

Jack DB (1997). One hundred years of aspirin. *Lancet*, **350**: 437-439.

Jafar TH, Jafary FH, Jessan S and Chaturvedi N (2005). Heart disease epidemic in Pakistan: Women and Men at equal risk. *Am. Heart J.*, **150**: 221-226.

Kong DF (2004). Aspirin in cardiovascular disorders. What is the optimum dose? *Am. J. Cardiovasc. Drugs*, **4**(3): 151-8.

Pappas JM, Westengard JC and Bull BS (1994). Population variability in the effect of aspirin on platelet function. Implications for clinical trials and therapy. *Arch. Pathol. Lab. Med.,* **118**: 801-804.

Rotameter KH (1991). Effects of acetylsalicylic acid in stroke patients. Evidence of non-responders in a subpopulation of treated patients. *Thromb. Res.,* **63**: 587-593.

Sadiq PA, Puri A, Dixit M, Ghatak A, Dwivedi SK, Narain VS Saran RK, Puri VK (2005). Profile and prevalence of Aspirin resistance in Indian patients with coronary artery disease. *Indian Heart J.*, **57**: 658-661.

Valles J, Santos MT, Aznar J Osa A, Lago A, Cosin J, Sanchez E, Broekman MJ and Marcus AJ. (1998). Erythrocyte promotion of platelet reactivity decreases the effectiveness of aspirin as an antithrombotic therapeutic modality: the effect of low-dose aspirin is less than optimal in patients with vascular disease due to prothrombotic effects of erythrocytes on platelet reactivity. *Circulation,* **97**: 350-355.

Vejar M, Vejar M, Fragasso G, Hackett D, Lipkin DP, Maseri A, Born GV, Ciabattoni G and Patrono C (1990). Dissociation of platelet activation and spontaneous myocardial ischemia in unstable angina. *Thromb. Haemost.,* **63**: 163-168.