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ASPIRIN RESISTANCE: AN EMERGING THREAT TO CARDIOVASCULAR DISEASE PATIENTS AND ITS ASSOCIATION WITH AGE AND GENDER

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Contribution

MN conceived the idea. UN planned the study. IF & AW drafted the manuscript. All the author contributed significantly in manuscript submission.

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ABSTRACT

Objective: To examine the existence of pharmacological aspirin resistance and its association with age and gender in cardiovascular disease patients.

Methodology: This cross sectional study was conducted from October 2015 to December 2016 at Pharmacology department Army Medical College, National University of Medical Sciences (NUMS), Rawalpindi in collaboration with Armed Forces Institute of Cardiology and National Institute of Heart Diseases (AFIC-NIHD) and Armed Forces Institute of Pathology (AFIP), Rawalpindi. Platelet function was analyzed by light transmission aggregometry (LTA) using arachidonic acid as an agonist. Data was analyzed by using SPSS version 23. Chi-square test and students t test was applied to evaluate the categorical and numerical variables respectively.

Results: Total of 384 cardiovascular patients meeting the explicit inclusion criteria were enrolled.There were 272 (70.8%) male and 112 (29.2%) female patients with the mean age of 48.22 ± 11.87 years. The statistical analysis revealed 13.8% (n = 53) aspirin resistant cases in study population with 14.7 % (n = 40) male and 11.6% (n=13) female (mean age 49.87 ± 13.20 years) were found to be aspirin non responders.

Conclusion: Our study suggests that phenomenon of aspirin resistance does exist in Pakistani population, and it is not modulated by age and gender of patients.

Key Words: Aspirin resistance, aspirin non responders, IHD, age, gender, LTA

INTRODUCTION

Atherosclerosis has a well established association with the development of ischemic vascular events like angina, myocardial infarction (MI), transient ischemic attacks (TIA) and ischemic strokes. Due to the pivotal role of platelets in acute thrombus progression, the anti platelet agents have become the leading drugs in the prescription of such patients.[1] Since the advent of anti platelet effects of aspirin, this wonder drug is enjoying the leading position among all the remedies of this category. The regular use of antiplatelet doses of acetyl salicylic acid has shown 40% reduction in risks of mortality from ischemic cardiovascular events.[2] The success story of aspirin lies on the fact that it permanently halts the production of thromboxane A2 (TXA2), a potent vasoconstrictor and platelet aggregator, by irreversible acetylation of platelet cyclooxygenase 1 (COX1) enzyme. This dose dependent inhibition of COX1 is swift, irretrievable and lasts for the life of platelet.[3] Despite the proven efficacy of aspirin in ischemic vascular disorders, yet not all the patients enjoy the beneficial out comes and experience frequent episodes of undesirable cardiovascular events. This phenomenon is generally known as Aspirin Resistance (AR) or aspirin treatment failure.[4] There is considerable variation in existence of AR in different populations. Two of the studies done in Pakistan revealed 12 to 47.1% AR among patients taking aspirin.[5,6]

Studies have shown that patients with poor response to aspirin are at greater risk of dreadful cardiovascular out comes like repeated attacks of myocardial ischemia and infarction.[7,8] Age and gender are among those various factors which can lead to low aspirin efficacy as indicated in recent researches.[9,10]

METHODOLOGY

It was a cross sectional study, conducted from October 2015 to December 2016 at Pharmacology department Army Medical College, National University of Medical Sciences (NUMS), Rawalpindi in collaboration with Armed Forces Institute of Cardiology and National Institute of Heart Diseases (AFIC-NIHD) and Armed Forces Institute of Pathology (AFIP), Rawalpindi. AFIC-NIHD and AFIP are the tertiary care facilities serving medical care to armed forces as well as civil population of diverse racially and ethnic groups from all over the Pakistan.

The sample size was calculated by using WHO statistical software. Patients of either sex, aged between 18 to 70 years, with cardiovascular diseases from outpatient department (OPD) as well as wards, belonging to each province of the country for representation of all major regions of Pakistan, were enrolled by non probability purposive sampling after written consent. The patients concurrently using other anti platelets or anti coagulants, having any bleeding disorder or platelet count $<150 \times 10^3$ cells/mm^3 were excluded.[11]

The study protocol was approved by Ethical Committee of Centre for Research in Experimental and Applied Medicine (CREAM) Army Medical College as well as Institutional Ethical Review Board (IERB) of AFIC-NIHD Rawalpindi.

Blood samples of 4.5 ml were collected after 2-12 hrs after the last dose and were stored in green caped conical tube, containing 0.5 ml of trisodium citrate for anticoagulation, were transported to hematology department AFIP for Platelet aggregation studies.

After complete blood count the samples were given a 10 minutes spin at 800 rpm to get native platelet rich plasma (PRP) and further centrifuged for 5 minutes at 4000 rpm to extract platelet poor plasma (PPP). The amount of platelet in PRP was managed in the range of 200 x $10^3/\mu$l to 350 x $10^3/\mu$l by utilizing PPP. Platelet aggregation studies were performed on Chrono-Log Aggregometer (Chrono-log, Havertown, Pa., USA) by using Arachidonic acid (0.5mM) as an agonist. Results were obtained in the form of graph on the completion of test. All this procedure was completed within three hours of sampling. Graphs showing Ý 20% platelet aggregation were labeled as aspirin resistant.[12]

The results were statistically analyzed by using Statistical Product and Service Solutions (SPSS) version 23.0 and presented in Mean±SD (standard deviation) and percentage. Chi-square test and students t test was utilized to evaluate the categorical and numerical variables respectively. $P < 0.05$ was considered as significant.

RESULTS

A total of 384 patients were included. Our sample population contained 272 (70.8%) males and 112 (29.2%) females with the mean age of 48.22±11.87 years. The statistical analysis revealed 13.8 % (n = 53) aspirin resistant patients where as remaining 86.2 % (n = 331) individuals had good efficacy of aspirin (Figure 1). Almost 85.3% (n = 232) of males and 88.4% (n=99) of females were enjoying the beneficial effects of aspirin as compare to the 14.7 % (n = 40) male and 11.6% (n=13) female who were found to be aspirin non responders (Figure 2). The mean age of responders was 48.41 ± 12.08 years and resistant 49.87±13.20 years (Figure 3). There was no statistical significant difference ($p > 0.05$) in existence of aspirin resistance in either sex, similarly our study could not found considerable association among aspirin response and age of patients when assessed by chi square test and independent sample test respectively. There was noteworthy discrepancy in the mean platelet aggregation between the aspirin resistant (60.19%±18.28%) and responders (3.28%±2.77%) with $p < 0.05$ as revealed by independent sample test.

Figure1: Aspirin Resistant and Responders in Study Population (n=384)

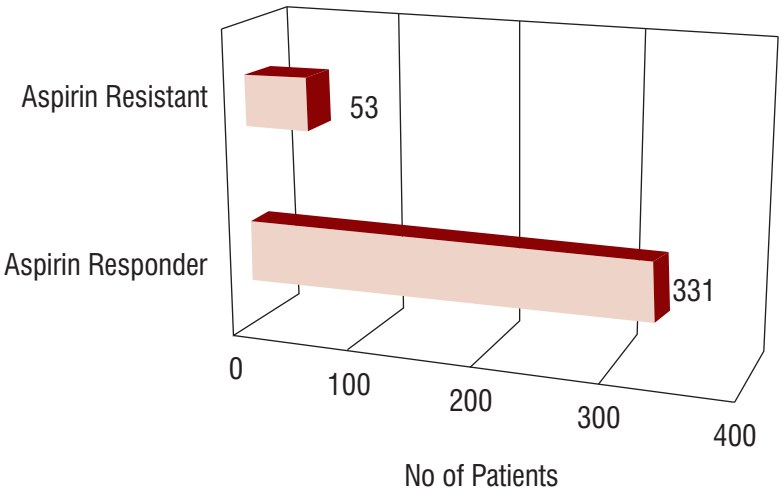


Figure 2: Male/Female Aspirin Responders and Resistant Patients(n=384)

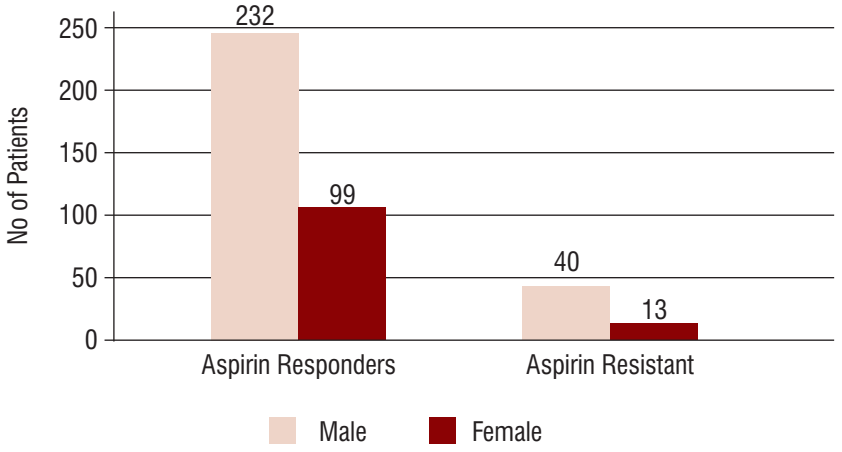
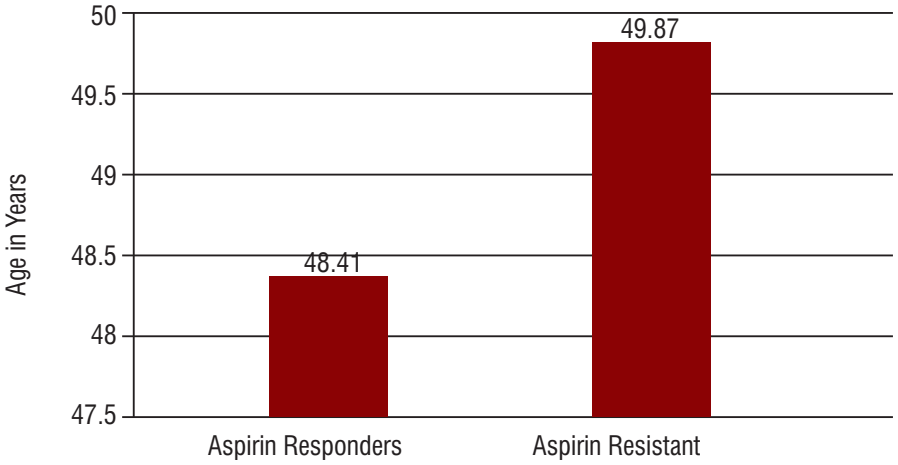


Figure 3: Average Age of Aspirin Responders and Resistant Patients(n=384)



DISCUSSION

Aspirin treatment failure or aspirin resistance is an emerging entity with considerable serious consequences. Literature review indicates high variability (4-45%) in prevalence of AR among different populations. One possible reason of this augmented inconsistency is diverse methods used for the assessment of AR by different researchers.[1-4] Our work revealed 13.8%(53/384) patients of cardiovascular diseases were not responding to aspirin when evaluated by LTA with AA which is considered gold standard method globally.

To the best of our knowledge only two studies conducted on Pakistani population to explore the AR. Naveed et al reported 12% aspirin resistance in their study conducted on 250 cardiovascular patients (73.2% male and 26.8% female with mean age 57.2 years).[5] On the other hand, Faheem et al carried out their work on 136 subjects (58.8% male and 41.25 female with mean age 52.66 years) and revealed 47.10% AR. IMPACT-R and Whole Blood Aggregometry was used to assess the aspirin effect by them respectively.[6] There was no statistical difference of age and gender on AR in both of above studies. These findings were consistent with our results.

Three of the studies conducted in recent past documented high prevalence of aspirin resistance. Luxmi et al, chadha et al and Salah et al discovered 23.7%, 36% and 48% of AR in their patients (76, 126 and 50) respectively.[1,3,13] All of these studies examined the platelet functions on LTA, luxmie et al used only ADP whereas Salah et al made use of only AA and chadha et al utilized ADP as well as AA as an agonist.[1,3,13] There was no association of gender with AR in these studies, however luxmi et al concluded that increase age predisposes the development of AR.[3] Similarly, Vaturi et al concluded the significant association of age with aspirin response, they found patients of Ý 75 years have more chances of AR, nonetheless no relation was established among gender in their study conducted on 583 stable ischemic heart disease patients.[9] They utilized VerifyNow Aspirin test to evaluate the aspirin response.

Becker et al performed platelet aggregation studies with different agonists on 711 female and 571 male cardiovascular patients at pre and post 14 days of aspirin treatment.[14] There was near complete inhibition of platelet aggregation observed in male upon exposure of epinephrine, ADP and collagen, however noteworthy platelet response was appreciated in women despite the daily aspirin dose. Surprisingly, both genders illustrated significant platelet aggregation on addition of arachidonic acid, signifying the role of additional pathways other than COX-1 in platelet function.[15] These findings were consistent with a randomized placebo-controlled trial of low dose aspirin treatment in the Women's Health Study (WHS) conducted on 39,876 women, which revealed almost 24% decline in risk of stroke with aspirin when compared with placebo but on the whole no decline in cardiovascular events was observed.[16] Moreover, another study titled as Hypertension Optimal Treatment (HOT) showed aspirin therapy effectively reduced MI risk by 42% in men whereas no decline was observed in women.[17] Sadiq et al, in his study reported very small number of Aspirin non responders i.e 2.08%.[18] They also suggested that female patients are more prone to acquire AR.

Yerman et al accentuated the importance of gender, age and ethnicity and documented the consideration of these variables in the assessment of AR in their meta analysis carried out on 23 randomized placebo-controlled trials including 113494 participants.[19] They used weighted linear regression technique to establish the association among long-transformed relative risk of myocardial infarction and the percentage of male/female contributors in each trial. Scrutiny of these studies revealed the significant risk reduction in non fatal MI among those trials whose majority of participant were male where as female dominated trials could not reproduce similar results. Their outcome supported the hypothesis that male might be more responsive to aspirin than female and consequently women are at higher risk of aspirin resistance.

CONCLUSION

AR is an emerging threat to cardiovascular disease patients that may result in treatment failure and ultimately ends up in serious adverse consequences. There may be various potential causes associated with different biochemical and demographic aspects including age and gender. Further studies with even larger number of patients are required to explore mechanistic explanations and clinical implications of this phenomenon.

REFERENCES

1. Salah A, El-Desuky M, Rizk A, El-Hadidy A. Aspirin resistance: prevalence and clinical outcome in Egypt. Egypt J Crit Care Med 2015;3(1):23-7.
2. Ahluwalia K, Bhanwra S. Antiplatelet therapy: present status and its future directions. Int J Basic Clin Pharmacol 2014;3:260-8.
3. Laxmi SS, Virendra A, Rajesh V, Ashutosh K, Jyotsana S, Isha A. Prevalence of aspirin resistance in patients with ischemic stroke at a tertiary care center in north India. J Med Sci Clin Res 2015;3(3):4684-6493.
4. Kasmeridis C, Apostolakis S, Lip GY. Aspirin and aspirin resistance in coronary artery disease. Curr Opin Pharmacol 2013;13(2):242-50.
5. Akhtar N, Junaid A, Khalid A, Ahmed W, Shah MA, Rahman H. Report: frequency of aspirin resistance in patients with coronory artery disease in Pakistan. Pak J

Pharm Sci 2009;22(2):230-3.

6. Faheem M, Ali J, Shah I, Samiullah, Hameedullah, Asghar M, et al. Frequency of aspirin resistance in patients with cardiovascular diseases. J Postgrad Med Inst 2012;26(4):356-62.
7. Eikelboom JW, Hirsh J, Weitz JI, Johnston M, Yi Q, Yusuf S. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. Circulation 2002;105(14):1650-5.
8. Gum PA, Kottke-Marchant K, Welsh PA, White J, Topol EJ. A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. J Am Coll Cardiol 2003;41(6):961-5.
9. Vaturi M, Vaduganathan M, Bental T, Solodky A, Kornowski R, Lev EI. Relation of aspirin response to age in patients with stable coronary artery disease. Am J Cardiol 2013;112(2):212-6.
10. Breet N, Sluman M, van Berkel M, Van Werkum J, Bouman H, Harmsze A, et al. Effect of gender difference on platelet reactivity. Neth Heart J 2011;19(11):451-7.
11. Fan L, Cao J, Liu L, Li X, Hu G, Hu Y, et al. Frequency, risk factors, prognosis, and genetic polymorphism of the cyclooxygenase-1 gene for aspirin resistance in elderly Chinese patients with cardiovascular disease. Gerontology 2013;59(2):122-31.
12. Lordkipanidze M, Pharand C, Schampaert E, Turgeon J, Palisaitis DA, Diodati JG. A comparison of six major platelet function tests to determine the prevalence of aspirin resistance in patients with stable coronary artery disease. Eur Heart J 2007;28(14):1702-8.
13. Chadha D, Sumana B, Karthikeyan G, Jayaprasad V, Arun SS. Prevalence of aspirin resistance in Asian?Indian patients with stable coronary artery disease. Cathet Cardiovasc Interv 2016;88(4): E126-31.
14. Becker DM, Segal J, Vaidya D, Yanek LR, Herrera-Galeano JE, Bray PF, et al. Sex differences in platelet reactivity and response to low-dose aspirin therapy. JAMA 2006;295(12):1420-7.
15. Fitzgerald R, Pirmohamed M. Aspirin resistance: effect of clinical, biochemical and genetic factors. Pharmacol Ther 2011;130(2):213-25.
16. Ridker PM, Cook NR, Lee I-M, Gordon D, Gaziano JM, Manson JE, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352(13):1293-304.
17. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351(9118):1755-62.
18. Sadiq P, Puri A, Dikshit M, Ghatak A, Dwivedi SK, Narain VS, et al. Profile and prevalence of aspirin resistance in Indian patients with coronary artery disease. Indian Heart J 2005;57(6):658-61.
19. Yerman T, Gan WQ, Sin DD. The influence of gender on the effects of aspirin in preventing myocardial infarction. BMC Med 2007;5:29.