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ORIGINAL ARTICLE

Evaluation of Pharmacological Aspirin Resistance and their Association with Gender and age in patients with Cardiovascular Disease

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ABSTRACT

Background: Atherosclerosis is widely known to increase the risk of developing ischemic vascular events such as angina, transient ischemic attack, myocardial infarction and ischemic strokes. By using various methodologies aspirin resistance ranges from 0.8 to 70.1 %.

Objective: The objective of current study was evaluation of pharmacological aspirin resistance and their association with gender and age in patients with cardiovascular disease

Methodology: The study design was cross sectional, done at the Department of Pharmacology, Bacha Khan Medical College, Mardan for duration of one year from January 2021 to January 2022. Chrono-Log Aggregometer ("Chrono-log, Havertown, Pa., USA") was used to study platelet aggregation utilizing Arachidonic acid of 0.5mM as an agonist. All the analysis of data was carried out by employing IBM SPSS version 24.

Results: In the current research, a total of 350 patients were enrolled. There were 238 (68%) males and 112 (32%) females. Based on the status of aspirin resistance, 51 (14.57%) participants show aspirin resistance. In the current study, statistically no significant association of aspirin resistance was observed with both age and gender (p>.05).

Conclusion: According to our findings, aspirin resistance is a growing concern in individuals with cardiovascular disease which might lead to failure of treatment and substantial side effects. There might be a variety of probable reasons linked to numerous biochemical and demographic factors, such as age and sex. To investigate mechanistic causes and clinical consequences of this phenomenon, more research with a large sample size is needed.

Key words: Pharmacological; Aspirin resistance; Cardiovascular disease

INTRODUCTION

Atherosclerosis is widely known to increase the risk of developing ischemic vascular events such as angina, transient ischemic attack, myocardial infarction (MI) and ischemic strokes. Anti-platelet medicines have been the most often prescribed medications for patients with acute thrombus because of platelets' critical involvement in thrombus development [1]. Aspirin has been a wonder drug ever since it was discovered that it can reduce the number of blood clots. This makes it the best remedy in this category. The administration of antiplatelet dosages of acetyl salicylic acid on a daily basis has been found to reduce the risk of death from ischemic cardiovascular events by 40% [2].

Aspirin is a potent antiplatelet drug that works by inhibiting platelet cyclooxygenase-1 enzyme irreversibly, reducing the synthesis of thromboxane A2 To prevent thromboembolic vascular events in both primary and secondary prophylaxis, it has been utilized [3, 4]. According to the Antithrombotic Trialists' Collaboration, aspirin was supportive in the majority of patients at high risk of occlusive vascular events, such as those who had a recent or prior myocardial infarction, stroke, unstable/stable angina, cerebral ischemia, atrial fibrillation and peripheral arterial disease [5]. Patients using 75–150 mg aspirin daily had a 32% lower risk vascular mortality, nonfatal stroke, nonfatal myocardial infarction and according to the meta-analysis [5]. Regardless of the fact that there is considerable argument in support of aspirin usage, it does not reduce thrombotic events in some people. Aspirin treatment does not work well for these people. "Aspirin resistance" is the term given to this problem [6]. When various methodologies are used to evaluate aspirin resistance, the frequency ranges from 0.8 to 70.1 % [7, 8]. Regrettably, a meta-analysis found that individuals who are aspirin resistant had a 2.85-fold increased chance of cardiovascular problems in comparison to those who are sensitive to aspirin [9]. Disagreement, insufficient dosage, concurrent therapy, enhanced platelet function and thromboxane generation, severity of CVD, smoking, hyper-glycemia, hypertension, hyperlipidemia, and genotypic variability are all potential causes of aspirin resistance [7, 8, 10-12].

The prevalence of aspirin resistance varies greatly across various groups. In two investigations conducted in Pakistan, aspirin resistance was found in 12 to 47.1 percent of individuals using aspirin [13, 14].

According to studies, people who have a poor reaction to aspirin are more likely to have severe cardiovascular consequences such as recurring episodes of myocardial ischemia and stroke. According to recent studies, age and gender are amongst the several characteristics that might contribute to decreased aspirin effectiveness.

Gender is one possible influential factor. There is growing concern that women are more likely than males to develop aspirin resistance, perhaps rendering aspirin lesser efficient in women [15]. Furthermore, women that acquire atherosclerosis are often older, suffer from a greater number of co-morbid illnesses, and have a more severe disease at the time of diagnosis, all of which may impair the effectiveness of aspirin [15]. This research looked at the occurrence of pharmacological aspirin resistance in cardiovascular disease patients, as well as its relationship with age and gender.

MATERIALS AND METHODS

The study design was cross sectional, piloted at the Department of Pharmacology, Bacha Khan Medical College, Mardan. The duration of study was one year from January 2021 to January 2022. A total of 350 subjects were enrolled in the current study. The criteria for inclusion in our study was all the subjects of both the sex having age 18-70 years from both the wards and outpatient department having cardiovascular problems. The criteria for exclusion in the current study was all the participants already on anti coagulants or anti platelets medication, patients having bleeding disorders and patients with platelet level less than 150000 cells/mm. In the current study non probability purposive sampling method was used. The study was approved properly the ethical and research committee of the institution. Informed consent was signed from all the subjects in written.

In this study, 5ml blood samples were obtained between 2 and 12 hours after the previous dosage and kept in a green caped conical tube that contains 0.5% trisodium citrate as anticoagulant. The samples were then transferred to the department of hematology of the hospital laboratory for platelet aggregation tests.

Following a full blood count, the samples were spun for 10 minutes at 800 rpm to obtain native platelet rich plasma, and then centrifugation was done for 5 minutes at 4000 rpm to obtain platelet poor plasma. Using platelet poor plasma, the quantity of platelets in platelet rich plasma was controlled between 200 and 350 x 10^3/µl. The Chrono-Log Aggregometer ("Chrono-log, Havertown, Pa., USA") was used to study platelet aggregation utilizing Arachidonic acid of 0.5mM as an agonist. On completion of the testing, the findings were presented in the form of a graph. Within 3 hours of sampling, the whole technique was performed. Aspirin resistance was defined as graphs presenting less than 20% platelet aggregation. All the analysis of data was carried out by employing IBM SPSS version 24. Percentages and frequencies were used for computation of categorical variables whereas continuous variables were determined in the form of mean and standard deviation. For association of aspirin resistance with age and gender, Chi-square test was used.

RESULTS

In the current research, a total of 350 cardiovascular patients fulfilling the inclusion criteria were enrolled in the study. There were 238 (68%) males and 112 (32%) females in the study. (Figure 1) The mean age in our study was 46.12 years with standard deviation of ±9.10. Based on the status of aspirin resistance, 51 (14.57%) participants show aspirin resistance whereas in 299 (85.43%) individuals, aspirin shows good efficacy. (Figure 2) The status of aspirin resistance, on the basis of gender, 17 (15.18%) females were resistant to aspirin and 95 (84.82%) females show good aspirin efficacy while 31 (13.02%) male have aspirin resistance and 207 (86.97%) males show good aspirin efficacy (p=0.321). (Figure 3) Based on age, aspirin resistance was observed in patients with mean (SD) age of 47.12 (8.23) years while the mean (SD) age in cardiovascular patients with good efficacy of aspirin was 45.23 (8.9) years (P=0.981). (Figure 4) In the current study, statistically no significant association of aspirin resistance was observed with both age and gender (p>.05).

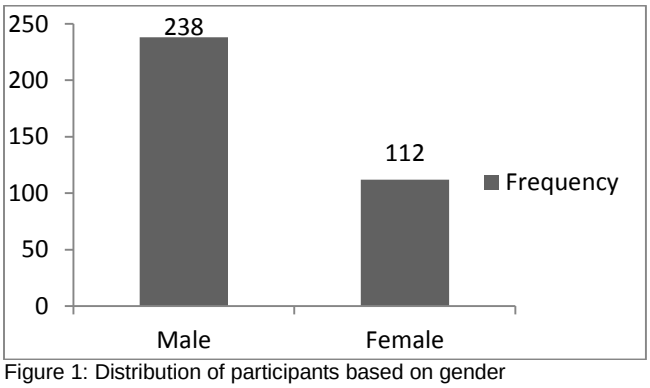

Figure 1: Distribution of participants based on gender

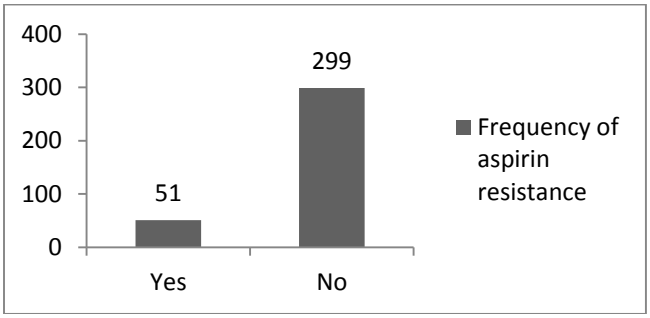

Figure 2: Frequency of participants with aspirin resistance

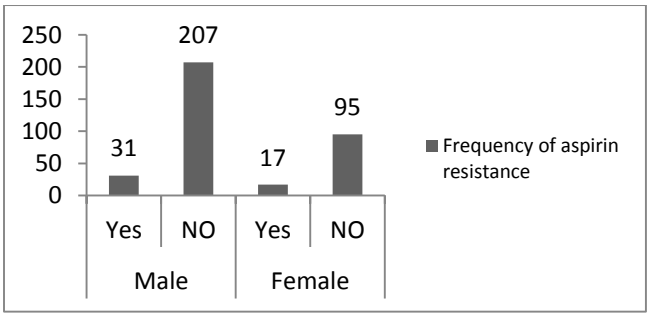

Figure 3: Gender based distribution of aspirin resistant and aspirin respondent

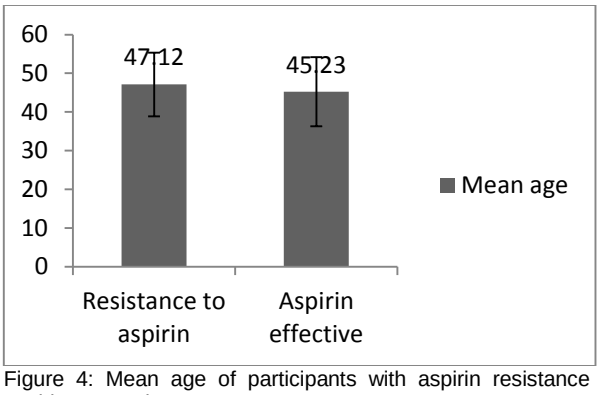

Figure 4: Mean age of participants with aspirin resistance and aspirin respondent

DISCUSSION

Aspirin treatment failure, often known as aspirin resistance, is a new phenomenon with dangerous repercussions. According to a study of the literature, the frequency of aspirin resistance varies greatly (4 to 45%) across various groups. Diverse methodologies employed by various studies to determine aspirin resistance might be one cause for the increased discrepancy [1, 2, 16, 17].

Based on the status of aspirin resistance, 14.57% participants show aspirin resistance whereas in 85.43% individuals, aspirin shows good efficacy in our study. We used a globally gold standard method of light transmission aggregometry with arachidonic acid. Only two studies have been undertaken on the Pakistani population to investigate aspirin resistance, according to the literature. One of the two studies was conducted by Naveed et al. on 250 patients with cardiovascular problems in Pakistan. There were 73.2% male and 26.8% female with mean (SD) age 57.2 (12.24) years in their study. They reported that 12% participants in their study were aspirin resistant which is comparable to our study [18]. Another study carried out Faheem et al. on 136 patients with cardiovascular problems in Pakistan. There were 58.8% male and 41.2% female with mean (SD) age 52.66 (12.24) years in their study. They reported that 47.10% participants in their study were aspirin resistant which is not in accordance with our study [13]. This might be due to the different procedure used to determine the aspirin resistance because they use IMPACT-R and Whole Blood Aggregometry to determine aspirin resistance while we use light transmission aggregometry with arachidonic acid.

The status of aspirin resistance, on the basis of gender, 15.18% females were resistant to aspirin and 84.82% females show good aspirin efficacy while 13.02% male have aspirin resistance and 86.97% males show good aspirin efficacy in our study (p=0.321). Based on age, aspirin resistance was observed in patients with mean (SD) age of 47.12 (8.23) years while the mean (SD) age in cardiovascular patients with good efficacy of aspirin was 45.23 (8.9) years (P=0.981). In the current study, statistically no significant association of aspirin resistance was observed with both age and gender (p>.05). These findings are in accordance with the previous studies who reported no significant association of aspirin resistance with gender and age [13, 18].

A study reported 23.7% prevalence of aspirin resistance which is not in accordance with our results. They used light transmission aggregometry with adenosine diphosphate as agonist. They reported no no significant association of aspirin resistance with gender and age [19]. A study carried out by Chadha et al. reported 36% prevalence of aspirin resistance which is not similar with our results. They used light transmission aggregometry with arachidonic acid as agonist. They reported no no significant association of aspirin resistance with gender and age [20]. Another study carried out by Salah et al, on 50 subjects reported 48% prevalence of aspirin resistance which is not in accordance with our results. They used light transmission aggregometry with both adenosine diphosphate and arachidonic acid as agonist. They came to the conclusion that as people become older, they are more likely to acquire aspirin resistance [16].

In a research on 583 patients with stable ischemic heart disease, Vaturi and their colleagues identified a significant link between age and aspirin responsiveness, finding that patients over 75 years old had a higher risk of aspirin resistance. However, no link was observed between gender and aspirin resistance. To assess the aspirin response, they used the Verify Now Aspirin test [19].

Becker et al. conducted platelet aggregation experiments with various agonists (711 female and 571 male cardiovascular patients) before and after 14 days of aspirin administration in a randomized clinical study[21]. When males were exposed to adenosine diphosphate, epinephrine and collagen, platelet aggregation was almost completely inhibited; but, with the daily aspirin dosage, women had a notable platelet response. Interestingly, both genders showed considerable platelet aggregation when arachidonic acid was added, indicating that platelet function is influenced by additional routes other than COX-1 [10].

A study done by Sadiq et al. reported a very low prevalence (2.08%) of aspirin resistance as compared to our study. They also claimed that women are more likely to develop aspirin resistance [22]. In the meta-analysis of 23 randomized placebo-controlled studies with 113494 individuals, Yerman et al emphasized the relevance of sex, age, and race and highlighted the incorporation of these factors in the evaluation of aspirin resistance [23]. They employed a weighted linear regression approach to find a link between long-transformed relative risk of MI (myocardial infarction) and the proportion of male and female participants in each experiment. These studies were analyzed, and it was shown that trials with a majority of male participants had a significantly lower risk of nonfatal MI, but female-dominated trials could not replicate comparable findings. Their findings backed with the theory that males are more reactive to aspirin as compared to women, putting women at a greater risk of developing aspirin resistance.

CONCLUSION

According to our findings, aspirin resistance is a growing concern in individuals with cardiovascular disease which might lead to failure of treatment and substantial side effects. There might be a variety of probable reasons linked to numerous biochemical and demographic factors, such

as age and sex. To investigate mechanistic causes and clinical consequences of this phenomenon, more research with a large sample size is needed.

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