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Original Research Article

Factors Causing Aspirin Resistance in Patients of Acute Coronary Syndrome in Central India: A Cross Sectional Study

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Abstract: ***Background:*** The mainstay of acute and long-term Management of Acute coronary syndrome includes aspirin and a P2Y12 inhibitor, such as clopidogrel or ticagrelor. Aspirin is a drug that has proved its efficacy in the treatment of various diseases in last 120 years and has stood the test of time. The challenge posed today is the variability in response to anti-platelet therapy which has been documented by many studies. The prevalence of resistance to aspirin is around 5%-45% worldwide. Hence, a study was planned to evaluate the factors causing aspirin resistance among the patients of acute coronary syndromes who were receiving of aspirin as anti-platelet drug therapy in our setting. ***Methods***: A cross sectional, observational study was conducted in a tertiary care rural hospital in central India. Patients of acute coronary syndrome or follow up cases of acute coronary syndrome, who were prescribed aspirin for at least 7 days as antiplatelet therapy, were included in the study. The aspirin resistance was documented in 46 (45.09%) patients by a test based on the plateletworks kit. The factors causing aspirin resistance were evaluated. Statistical analysis was done by using descriptive and inferential statistics using chi square test and z-test. The statistical software used in the analysis was graph pad prism 5.0 and SPSS 17.0.***Results and conclusion:*** The patients receiving 150 mg of aspirin, hypertension, concurrent intake of beta-blockers or ARB, elevated level of LDL cholesterol had a trend to be more inclined towards aspirin responders while patients receiving 75 mg of aspirin, diabetes and addiction to tobacco or alcohol had a trend to be more aspirin resistant. Other parameters tested namely age, gender, BMI, Duration of treatment, smoking, concurrent intake of statins, calcium channel blockers, ACE inhibitors, diuretics or PPI, blood glucose level or cholesterol levels (except LDL) did not show any statistically significant difference among the aspirin responders or resistant groups.

Keywords: Aspirin resistance, Acute coronary syndrome, factors, India.

INTRODUCTION

The term "acute coronary syndrome" refers to a spectrum of conditions compatible with acute myocardial ischaemia and/or infarction that are usually due to a sudden reduction in coronary blood flow. The diagnosis of STEMI is based on clinical findings and on persistent ST-segment elevation on the electrocardiogram. Patients with STEMI should be treated immediately with reperfusion therapy, mainly primary angioplasty or thrombolysis. Primary angioplasty is the preferred treatment, but is not always available. Reperfusion therapy, with antiplatelet and anticoagulant medication, makes up the main therapeutic management (Foussas, S. 2015). Acute coronary syndrome (ACS) is a major health care and economic burden. The morbidity and mortality due to ACS are substantial. ACS causes half of all deaths due to coronary heart disease. As it is becoming a leading public health problem around the globe, it is not surprising that a vast part of the medical research is now focusing on the identification of genetic and environmental factors contributing to the development of this multifactorial disease (Franchini, M. 2016).

The mainstay of acute and long-term management includes aspirin and a $P2Y_{12}$ inhibitor, such as clopidogrel or ticagrelor (Kotecha, T., & Rakhit, R.D. 2016). Aspirin is a drug that has proved its efficacy in the treatment of various diseases in last 120 years and has stood the test of time (Walker, P. J. *et al*., 2018). Current guidelines recommend dual antiplatelet therapy for 1 year following ACS (Roffi, M. *et al*., 2016).

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The challenge posed today is the variability in response to anti-platelet therapy which has been documented by many studies (Foussas, S. 2015; Maree, A. O., & Fitzgerald, D. J. 2007). The fact that patients do land up with attacks of thrombo-embolic episodes in emergencies who were already receiving preventive therapy in terms of aspirin and/or clopidogrel, aiming to prevent such episodes, also suggest the prevalence of variability of responses to these drugs. Many studies have highlighted the emergence of aspirin resistance as an emerging entity. This is posing a therapeutic challenge in cardiovascular medicine today (Wang, T. H. *et al*., 2005; Guyer, K. E. 2009; Matetzky, S. *et al*., 2004).

In India, this topic of resistance to aspirin has been explored by cardiac physicians and researchers (Sadiq, P. A. *et al*., 2005; Kumar, S. *et al*., 2007; Thomson, V. S. *et al*., 2009; Guha, S. *et al*., 2009; Guha, S. *et al*., 2009). But studies are very few and there is still a need of further exploration

The term "resistance" is used here to denote the inadequate response or treatment failure because of various reasons like improper drug compliance or early discontinuation, possible drug interactions, inadequate dose, increased platelet turnover, genetic polymorphisms, potential bypass mechanisms and others (Guyer, K. E. 2009). Some use it to refer to the continued occurrence of ischemic events despite adequate anti-platelet therapy and compliance. With the objective tests availability, the term is getting evolved and also its implications too.

The prevalence of resistance to aspirin is around 5%-45% worldwide. In India, incidence of aspirin resistance was documented as 38.1 by Thomson *et al*., (2009). In Guha *et al*., (2009), aspirin resistance was encountered in 35% patients with recurrent ACS while in patients with first episodes of ACS was 25.3%.

The factors causing aspirin resistance and variability in response to aspirin are important to be identified. So, that we can prevent the significant mortality and morbidity caused by aspirin resistance.

Hence, a study was planned to evaluate the factors causing aspirin resistance among the patients of acute coronary syndromes who were receiving of aspirin as anti-platelet drug therapy in our setting. This study is a continuation of our previous study already published (Dhanvijay, P.V. *et al*., 2019).

MATERIAL AND METHODS

A cross sectional, observational study was conducted in a tertiary care rural hospital in central India. Patients attending medicine OPD or admitted to medicine wards with a diagnosis of acute coronary syndrome or follow up cases of acute coronary syndrome, who were prescribed aspirin for at least 7 days as antiplatelet therapy, were included in the study after obtaining their informed written consent and explaining the study objectives. The study period was January 2011 to May 2012. An ethical clearance from the Institutional Ethics Committee was obtained prior to the commencement of the study.

Inclusion criteria:

Patients with a diagnosis of acute coronary syndrome including ST elevated acute myocardial infarction (STEMI), Non-ST elevated acute myocardial infarction (NSTEMI) and unstable angina and follow up cases of the above diagnosis attending medicine OPD or getting admitted to medicine ward for it or other reasons and on aspirin for minimum of 7 days as antiplatelet therapy were included in the study.

Exclusion criteria:

The patients with one of the following were excluded from the study-

- Concurrent use of non-steroidal anti-inflammatory drugs.
- Family or personal history of bleeding disorders.
- Platelet count < 150 x 10^3 /L or > 450 x 10^3 /L.
- Consent not given for participation in the study.

Around 110 patients were screened, out of which 8 patients were excluded as 3 of them had thrombocytopenia (platelet counts less than 150 x 10^3) while 5 patients refused consent. Hence, 102 patients were included in the study.

The data was collected in a questionnaire which included demographic details of the patient, medical history, medication history and biochemical details along with the report of blood sample collected for evaluation of aspirin resistance. The aspirin resistance was documented in 46 (45.09%) patients (Dhanvijay, P.V. *et al*., 2019) by a test based on the plateletworks kit which was modified by Sushil *et al*., The factors causing aspirin resistance were evaluated.

Statistical analysis:

Statistical analysis was done by using descriptive and inferential statistics using chi square test and z-test. The statistical software used in the analysis was graph pad prism 5.0 and SPSS 17.0. The level of significance was 5%.

RESULTS

Out of 102 patients who were on aspirin as antiplatelet therapy, aspirin resistance was documented in 46 (45.09%) which included semiresponders and non-responders. Prevalence of aspirin resistance was the a part of this study which is already published.

Table 1: Grouping of patients according to the antiplatelet aggregation response of the study subjects on aspirin

Groups	Aspirin responder	Aspirin Semi-responder	Aspirin Non-responder	Total
Number of patients	56	25	21	102
		Aspirin Resistant - 46		

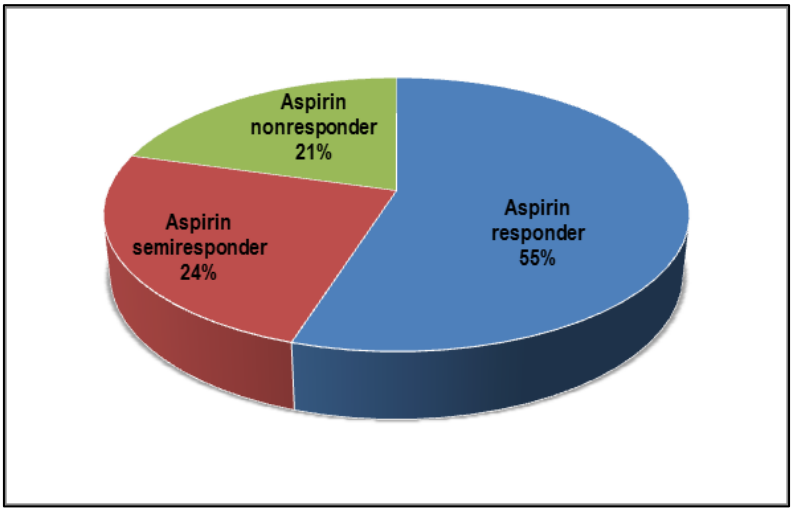

Figure 1: Grouping of patients on aspirin according to the response to aspirin

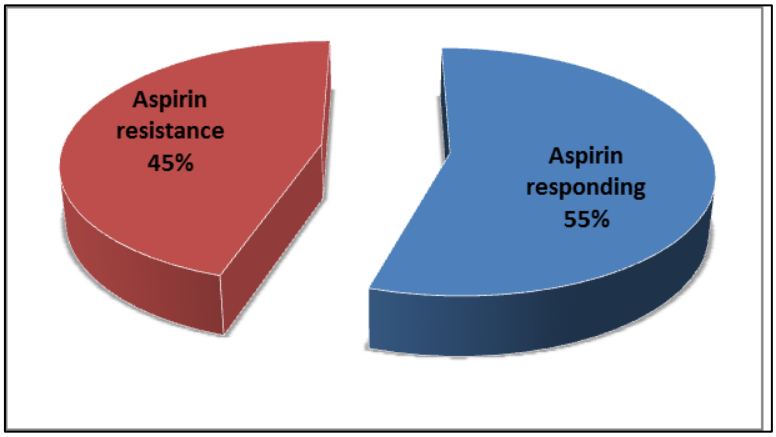

Figure 2: Grouping of patients responding to aspirin or resistance to aspirin Comparison of aspirin response groups in terms of demographic characteristics

Table 2: Comparison of demographic characteristics of aspirin response groups

Variables	Aspirin Responder (n=5	Aspirin Resisita (n=46)	p-value
Age (years)	59.67 ± 10.74	60.06 ± 11.50	0.862NS, p>0.05
Gender (M:F)	37:19	26:20	0.32NS, p>0.05
BMI (Kg/m2)	27.09 ± 3.61	26.90 ± 3.76	0.806NS, p>0.05

NS- not significant

Table 2 shows the demographic characteristics of aspirin responding and aspirin resistant groups. The mean age of the patients in the aspirin responder group was 59.67 ± 10.74 years, while the mean age in the aspirin resistant group was 60.06 ± 11.50 years. The difference between the mean ages was not statistically significant (p>0.05).

The aspirin response group had 37 (66%) males and 19 (34%) females, whereas the aspirin semi/non-responder group had 26 (57%) males and 20 (43%) females. The gender differences were not statistically significant (p>0.05).

The mean BMI in aspirin responder group and the aspirin semi/non responder group were 27.09 ± 3.61 and 26.90 ± 3.76 kg/m^2, respectively. The difference was not statistically significant (p>0.05).

Table 3: Comparison of the aspirin dose and duration in aspirin response groups

Variables	Aspirin Responding (n=56)	Aspirin Resistant (n=46)	p-value
Aspirin Dose 75 mg	42 (75%)	41 (89.13%)	0.01^S, p<0.05
Aspirin Dose 150 mg	14 (25%)	2 (4.35%)	p<0.0001 Significant
Aspirin duration (months)	11.07 ± 24.89	11.11 ± 12.76	0.99^{NS}, p>0.05

S-Significant, NS-Not significant

Table 3 shows the comparison medical history of aspirin response groups, namely, Aspirin responders Vs aspirin resistant. Out of 56, 42 (75%) of the aspirin responder group and out of 46, 41 (89.13%) of the aspirin resistant group received aspirin dose as 75 mg. The difference between the two groups was statistically significant.

Out of 56, 14 (25%) of the aspirin responder group and out of 46, only 2 (4.35%) of the aspirin resistant group received aspirin dose as 150 mg. The difference between the two groups was statistically significant (p<0.0001).

The mean duration of aspirin treatment in aspirin responder and aspirin resistant was 11.07 ± 24.89 and 11.11 ± 12.76 months, respectively and difference was not satistically significant.

Table 4: Comparison of the association with hypertension and diabetes mellitus in aspirin response groups

Variables	Aspirin Responding (n=56)	Aspirin Resistant (n=46)	p-value
Hypertension	29(51.79%)	21(45.65%)	0.39 NS, p>0.05
Diabetes mellitus	9(16.07%)	16(34.78%)	0.002 S, p<0.05

NS- Not Significant, S- Significant

Table 4 shows the comparison of the association with hypertension and diabetes mellitus in aspirin response groups namely, aspirin responders Vs aspirin resistant. 29 (51.79%) patients had hypertension in the aspirin resonder group, while 21 (45.65%) in the semi/non responder group and the difference was not satistically significant (p>0.05).

9 (16.07%) patients had diabeties mellitus in th aspirin responder group and 16 (34.78%) in the aspirin resisitant group. The difference between the two groups was staistically significant (p<0.05) suggesting a correlation between diabeties mellitus and aspirin resistance.

Table 5: Comparison of the association of addiction to smoking, tobacco and alcohol in aspirin response groups

Variables	Aspirin Responding (n=56)	Aspirin Resistant (n=46)	p-value
Smoking	10 (17.86%)	10 (21.74%)	0.47 NS,p>0.05
Tobacco	19 (22.93%)	19 (41.30%)	0.0006 S,p<0.05
Alcohol	0 (0.00%)	4 (8.70%)	0.002 S,p<0.05

NS- Not Significant, S- Significant

Table 5 shows the comparison of the association of addictions (smoking, tobacco and alcohol) in aspirin response groups namely, aspirin responders Vs aspirin resistant. In the aspirin responder group, 17.86% of patients (n=10) whereas in the resisitant group, 21.74% of patients (n=10) were smokers. The difference was not staistically significant (p>0.05).

19 (22.93%) out of 56 in the aspirin responder group while 19 (41.30%) out of 46 in the aspirin resistant group were tobacco addict. The difference between the two groups was staistically significant (p<0,05).

0 out of 56 in the aspirin responder group while 4 out of 46 in the aspirin resistant group were alcoholic. The difference was staistically significant (p<0.05).

Table 5: Comparison of aspirin response groups in terms of medication history

Variables	Aspirin Responding (n=56)	Aspirin Resistant (n=46)	p-value
Statins	54 (96.43%)	44 (95.85%)	1.00 NS, p>0.05
Beta-Blocker	29 (51.79%)	17 (36.96%)	0.032 S, p<0.05
Calcium channel blocker	10 (17.86%)	8 (17.39%)	1.00 NS, p>0.05
ACE Inhibitor	12 (21.43%)	10 (21.74%)	0.86 NS, p>0.05
ARB	40 (71.43%)	25 (54.35%)	0.010 S, p<0.05
Diuretics	9 (16.07%)	7 (15.22%)	0.82 NS, p>0.05
PPI	1 (1.79%)	2 (4.35%)	0.40 NS, p>0.05

NS- Not Significant, S- Significant

Table 5 shows the comparison of drug history in the aspirin response groups. Out of 56 in the aspirin responder group, 54 (96.43%), 29 (51.79%), 10 (17.86%), 12 (21.43%), 40 (71.43%), 9 (16.07%) and 1 (1.79%) took statins, beta-blocker, calcium channel blocker, angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), diuretics and proton pump inhibitor (PPI), respectively. Among the 46 of the resistant group, 44 (95.85%), 17 (36.96%), 8 (17.39%), 10 (21.74%), 25 (54.35%), 7 (15.22%) and 2 (4.35%) took statins, beta-blocker, calcium channel blocker, angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), diuretics and proton pump inhibitor (PPI), respectively. The difference in the two group was statistically non-significant (p>0.05) in all, except in patients who took beta-blocker (p<0.05) and ARB (p<0.05) along with aspirin.

Table 6: Comparison of test results of blood glucose in aspirin response groups

Variables	Aspirin Responding (n=56)	Aspirin Resistant (n=46)	p-value
Glucose Fasting	106.10 ± 28.42	112.34 ± 41.18	0.386 NS, p>0.05
Glucose PP	148.14 ± 37.99	157.76 ± 62.74	0.365 NS, p>0.05
RBS	138.32 ± 42.97	145.76 ± 76.10	0.557 NS, p>0.05

NS- Not Significant

Table 6 shows the comparison of blood glucose test results in aspirin response groups, namely, aspirin responders Vs aspirin resistant. The mean fasting, postprandial (PP) and random blood sugar (RBS) in the aspirin responder group were 106.10 ± 28.42, 148.14 ± 37.99 and 138.32 ± 42.97mg/dl, while that in the aspirin semi/non responder group were 112.34 ± 41.18, 157.76 ± 62.74 and 145.76 ± 76.10, respectively. The differences were statistically non-significant (p>0.05).

Table 7: Comparison of test results of lipid profile in aspirin response groups

Variables	Aspirin Responding (n=56)	Aspirin Resistant (n=46)	p-value
TC (mg/dl)	152.66 ± 40.10	158.80 ± 44.86	0.472 NS, p>0.05
HDL (mg/dl)	41.37 ± 13.48	46.45 ± 12.72	0.054 NS, p>0.05
TG (mg/dl)	128.28 ± 61.28	136.47 ± 74.19	0.550 NS, p>0.05
LDL (mg/dl)	97.87 ± 87.23	72.11 ± 34.64	0.047 S, p<0.05
VLDL (mg/dl)	26.64 ± 13.26	27.77 ± 15.21	0.694 NS, p>0.05

NS- Not Significant, S- Significant

The Table 7 shows the comparison of test results of lipid profile in aspirin response groups, namely, aspirin responders Vs aspirin resistant. The mean total cholesterol (TC), *high-density lipoprotein* (*HDL*), triglycerides (TG), *low-density lipoprotein* (*LDL*), *very low density lipoprotein* (VL*DL*) in the aspirin responder group were 152.66 ± 40.10, 41.37 ± 13.48, 128.28 ± 61.28, 97.87±87.23, and 26.64 ± 13.26 mg/dl, respectively, whereas that in the aspirin semi/non responder group were 158.80 ± 44.86, 46.45 ± 12.72, 136.47 ± 74.19, 72.11 ± 34.64 and 27.77 ± 15.21, respectively. The differences were statistically non- significant (p>0.05) except for LDL level which was statistically significant (p<0.05).

DISCUSSION

Oral antiplatelet drugs are the cornerstone of modern pharmacotherapy in cardiovascular atherothrombotic diseases. But despite chronic oral antiplatelet therapy, atherothrombotic events continue to occur in number of patients (Feher, G. *et al*., 2010).

A large proportion of patients at high risk of cardiovascular events do not benefit from aspirin antiplatelet therapy and implies that antiplatelet drugs fail to suppress their targets and thus in preventing cardiovascular events in patients because of various factors. Thus, witnessing the emergence of a new phenomenon of 'aspirin resistance' (Gasparyan, A. Y. 2010).

Studies have estimated a prevalence of aspirin resistance ranging from 5.5% to 60% (Gasparyan, A. Y. *et al*., 2008). This range is variable in different studies and this prevalence suggests that patients at risk who are taking aspirin as preventive therapy are still at risk despite of the fact that drugs are being prescribed to protect them.

Sharma *et al*., (2009) raised a vital question in his latest review as why monitoring is not done for platelet function in patients taking antiplatelet drugs as it is done for hypertensive patients on antihypertensive drugs or diabetic patients on antidiabetic drugs by blood pressure and glucose monitoring, respectively. It also presented several tests for tailoring antiplatelet therapy and stratified patients into non-responsive, hypo-responsive and responsive to aspirin. Various reasons not monitoring are non-availability of the instruments, very high costs of the tests, laborious technique, complex sample preparation, large volume of the sample required, non-availability of trained staff and many more.

We studied 102 patients of acute coronary syndrome of which 102 received aspirin and around 88 received clopidogrel. After evaluating the antiplatelet aggregation activity of the aspirin and clopidogrel in patients of acute coronary syndrome by a test which was adaptation of plateletworks kit, we found the prevalence of aspirin resistance as 45.09%.

A Meta analysis done recently showed that the prevalence of laboratory aspirin resistance ranged from 5% to 65%. Mean prevalence of aspirin resistance by various laboratory tests was found to be 27% (Snoep, J. D. *et al*., 2007).

Sadiq *et al*., (2005) evaluated prospectively aspirin resistance in Indian patients with stable coronary artery disease on 150 mg aspirin by platelet aggregometer. In their study aspirin resistance was seen in 2.08% of patients and 39.58% were semiresponders. H Mardikar *et al*., (Mardikar, H. *et al*., 2008).studied patients with CAD or stroke or transient ischemic attack or peripheral artery disease or with multiple atherothrombotic risk factors and were receiving aspirin 150 mg daily. In this study 3.1% were said to be hyporesponders.

The prevalence of residual platelet reactivity despite aspirin intake found in our study (45.09%) is close to as shown by Sadiq *et al*., (2005) (semiresponder and aspirin resistance-2.08%+39.58%=41.66%). The difference may be because the dose of aspirin used in our study was variable (75/150 mg) and doubling of dose of aspirin brings the semiresponders to responder group and hence reduces the aspirin resistance prevalence. Also, our study included patients who were follow up cases and hence non-compliance may be a big factor causing variation in the prevalence of resistance.

Guha *et al*., (2009) assessed both aspirin and clopidogrel resistance in patients with ACS in Indian population and found 17% of patients as aspirin resistant. They included patients who immediately after 7 days of starting the treatment and patients are more likely to be compliant in this phase of time period as they are hospitalized and medications are being given supervised and secondly because they have recently had a life threatening disease for which they are getting treated and hence they are more likely to have adherence to treatment (Ho, P. M. *et al*., 2006; Shantsila, E., & Lip, G. Y. 2008). Also, the dose used for in their study was 150mg aspirin.

Association of aspirin response with risk factors

There was no significant difference between the two groups according to the response to aspirin in relation to demographic features like age, gender or BMI. Gum *et al*., (2003) reported a trend towards increased age in patients with aspirin resistance or semiresponders. Our study didn't show such a trend as the study population was with a mean age approx 60 years.

In our study neither males nor females showed higher aggregation. This was not in coordination with Sadiq *et al*., (2005) and Gum *et al*., (2003) who have reported a higher degree of aspirin non responsiveness in females and Ashwin *et al*., (2007) who found higher aggregation in males.

The BMI of patients in both the groups was slightly on higher side with 27.09 ± 3.61 & 26.90 ± 3.76 in both the responder and resistant group, respectively. In our study, the patients receiving 75 mg of aspirin were less likely to be responder and who received 150 mg of aspirin were more likely to belong to the responder group. The difference in the two groups was statistically significant. Thomson *et al*., (2009) showed that overweight patients (who had BMI >24.99) had more aspirin resistance and commented that 75 mg aspirin per day may not be optimal in overweight Indian patient for secondary prevention. Guha *et al*., (2009) showed that they observed a satisfactory inhibition of platelet aggregation after doubling the maintenance dose of aspirin from 150 mg to 300 mg. Thus, suggesting inadequacy of the dose. It suggests that 75 mg of aspirin may not be adequate and patients who are semi responder while receiving 75 mg of dose might respond adequately if the dose is doubled.

Our study supports this fact as in 16 patients who were receiving 150 mg of aspirin per day, only 2 patients showed semi-non responsiveness and 14 responded well to the drug. This also highlights the need for calculating the dose as per body weight or BMI of the patient. If done so, chances of getting full response to the drug increases. But problem in calculation dose and prescribing so is challenged by the availability of low dose aspirin in two doses only, 75 mg and 150 mg. The 100 mg tablet of low dose aspirin should also be available.

Hung *et al*., (1995) showed that smoking-enhanced platelet thrombosis and suggested it to be an important contributory mechanism for acute coronary events in smokers that is not prevented by aspirin treatment. Catecholamine release and heightened platelet aggregation response to in vivo agonists was suspected to contribute to the prothrombotic effects of smoking.In our study we did not find any difference in the sensitivity to aspirin with respect to smoking and this was similar to Thomson *et al*., (2009) and Guha *et al*., (2019) aslo failed to show any statistical difference in smokers.

In our study we did found tobacco and alcohol addicts belonged more to resistant group. Guha *et al*., (2009) also tried to see sensitivity to aspirin with respect to tobacco addiction and found that they belonged more to the resistant group as in our study. This is in contrast to Wennmalm *et al*., (1991) who found that use of snuff (oral tobacco) does not facilitate the formation of thromboxane A2 as smoking does. We could not find any study correlating with alcohol. This difference may be because of less number of patients taking tobacco.

In our study, patients with diabetes mellitus were more likely to belong to the resistant group and the difference was statistically significant. This finding is similar to ASPECT study (2007) which found that diabetic patients exhibit higher platelet reactivity than non-diabetic patients.

Many evidences suggest that platelet hyperactivity is present in patients with diabetes and is mediated by insulin resistance and increased P2Y12 signaling. Other mechanisms include increased platelet turnover, altered membrance structure, increased intracellular calcium and abnormal glycation (Mehta, S. S. *et al*., 2006; Abaci, A. *et al*., 2005).

Also, diabetes is a prothrombotic state which is associated with increased in vivo formation of 8-iso-prostaglandin F2α formation. It is implicated that increased oxidative stress in diabetics causes incresed formation of these compounds. These compounds causes enhanced platelet activation (Davì, G. *et al*., 1999). This may be the reason that in our study blood glucose results (glucose fasting, PP or RBS) were lower in the responder group but statistical significance could not be established.

More of hypertensive patients belonged to aspirin responder group but the difference was statistically non-significant. Feher *et al*., (1998) who studied the presence of hypertension and aspirin resistance among patients with cardiovascular and cerebrovascular diseases on aspirin and found higher prevalence of hypertension among aspirin sensitive patients. Reasons suggested were higher rate of beta-blocker and ACE inhibitor usage as antihypertensive drugs as these drugs exert an additive antiplatelet action when combined with aspirin. But Guha *et al*., (2009) found aspirin resistance to be higher in hypertensive subjects.

In our study, we found also that patients taking betablockers belonged significantly to the responder groups. This may be because evidences say that betablocker do have antiplatelet aggregation activity of it own and can significantly inhibited thromboxane synthesis by their platelets and platelet aggregation induced by thrombin or arachidonic acid (Campbell, W. *et al*., 1981). Thus, it can enhance activity of aspirin.

ARB receiving patients significantly belonged more to aspirin responder group. This is supported by a study by Murad *et al*., (Murad, J. P. *et al*., 2012), who studied losartan, an ARB to investigate its potential in vivo antiplatelet and thromboprotective in mice. He found that it produces a thromboxane A2 receptor-specific antiplatelet effect which gets translated into thromboprotective properties, without resulting in a bleeding phenotype. He also suggested that losartan's chemistry may provide a "blueprint" for designing or repurposing novel derivatives which may have the potential to serve as an antiplatelet and thromboprotective agents but are deprived of the usually concomitant bleeding adverse effects.

But patients taking ACE inhibitors, calcium channel blockers or diuretics as antihypertensive medication did not show any difference in the two groups. Other medications taken along with antiplatelet drugs in our study included statins and PPI. Intake of both did not show any difference in sensitivity to aspirin. The findings are similar to Guha *et al*., (2009).

This is in contrast to Guha *et al*., (2009) who found that aspirin resistance was higher in patients having higher LDL. In our study, lipid profile results showed that patients had a lower level of TC, HDL, TG and VLDL in aspirin responder group but the difference was not significant whereas LDL was higher in responder group and the difference was statistically significant. Friend *et al*., (2003) found that aspirin may not be cardioprotective in patients with hyperlipidemia they had poor responsiveness to aspirin. Altman *et al*., (2004) found that patients with poor responsiveness to

aspirin had significantly higher total cholesterol and LDL patients. Mehta *et al*., (2006) studied aspirin resistance and found that low HDL levels were more likely to be aspirin sensitive. But aspirin resistance (AR) was not related to total cholesterol (Mehta, S. S. *et al*., 2006). Our study findings (Table 5.2) are supported by the above studies.

After comparing the aspirin responder and resistant groups, patients receiving 150 mg of aspirin, hypertension, concurrent intake of beta-blockers or ARB, elevated level of LDL cholesterol had a trend to be more inclined towards aspirin responders while patients receiving 75 mg of aspirin, diabetes and addiction to tobacco or alcohol had a trend to be more aspirin resistant.

Other parameters tested namely age, gender, BMI, duration treatment, smoking, concurrent intake of statins, calcium channel blockers, ACE inhibitors, diuretics or PPI, blood glucose level or cholesterol levels (except LDL) did not show any statistically significant difference among the aspirin responders or resistant groups

As the inclusion criteria was patients on aspirin prescription, so we could not assure compliance of the patients. Hence, non-compliance may be factor in the variability of responses to aspirin. For this further studies should be done to see the platelet function after assuring compliance of aspirin.

CONCLUSIONS

The patients receiving 150 mg of aspirin, hypertension, concurrent intake of beta-blockers or ARB, elevated level of LDL cholesterol had a trend to be more inclined towards aspirin responders while patients receiving 75 mg of aspirin, diabetes and addiction to tobacco or alcohol had a trend to be more aspirin resistant. Other parameters tested namely age, gender, BMI, duration treatment, smoking, concurrent intake of statins, calcium channel blockers, ACE inhibitors, diuretics or PPI, blood glucose level or cholesterol levels (except LDL) did not show any statistically significant difference among the aspirin responders or resistant groups.

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