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ORIGINAL ARTICLE

Association of clopidogrel resistance with ethnicity in Pakistan.

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ABSTRACT… Objective: To assess relationship between clopidogrel resistance and different ethnicities in Pakistan. **Study Design:** Cross-sectional study. **Setting:** Army Medical College, National University of Medical Sciences (NUMS), Pakistan. **Period:** 2015 to 2019. **Material & Methods:** Included 390 ischemic heart disease (IHD) patients on clopidogrel therapy belonging to different ethnicities in Pakistan. Their platelet aggregation was assessed through light transmission aggregometry and the patients were divided into clopidogrel responder and clopidogrel resistant groups. Chi square analysis was done to assess difference in clopidogrel resistance among different ethnicities. One-way ANOVA was applied to assess difference in mean platelet aggregation among different ethnic groups. **Results:** This study has demonstrated that there was no significant difference in clopidogrel resistance among ischemic heart disease patients belonging to different ethnic groups of Pakistan, $p = 0.566$. Mean platelet aggregation of all the ethnic groups was also similar, $p = 0.330$. **Conclusion:** There is no association of clopidogrel resistance with ethnicity in Pakistan.

Key words: Clopidogrel, Ethnicity, Pakistan.

INTRODUCTION

Clopidogrel is an antiplatelet drug with multiple clinical indications particularly related to ischemic heart diseases. Its function is to inhibit platelet aggregation, thus, reducing the chances of thrombus formation and propagation, and coronary artery stent occlusion after percutaneous coronary intervention.[1]

Clopidogrel is a second-generation thienopyridine which is basically a prodrug that is activated in the liver by cytochrome (CYP) enzymes into active metabolites. This is a two-step process and various cytochrome enzymes including CYP2C9, CP2C19, CYCP3A4 etc. take part in these reactions.[2]

After activation, clopidogrel performs its antiplatelet action by inhibiting adenosine diphosphate (ADP) receptors present on the surface of platelets. Normally, ADP stimulation is associated with platelet activation leading to platelet aggregation. There are two types of ADP receptors i.e., $P2Y_1$ and $P2Y_{12}$. Clopidogrel specifically blocks $P2Y_{12}$ ADP receptors.[3]

Antiplatelet action of clopidogrel is not persistent in all the patients due to varying degree of clopidogrel resistance that may exists in different individuals. Different causes have been attributed to clopidogrel resistance which may include population differences, genetic variations in clopidogrel metabolism, poor compliance and coadministration of proton pump inhibitor omeprazole.[4]

Epidemiological studies have shown that there is marked variations in events of ischemic heart diseases in different ethnic groups. Such variations may be related to differences in genetics, risk factors of ischemic heart diseases, and sociocultural environment.[5] Clopidogrel is an antiplatelet medication commonly used in the treatment of Ischemic Heart Disease (IHD), particularly in conditions like acute coronary syndromes (ACS) and after certain types of

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cardiac interventions like stent placement.[17,18] Its mechanism of action involves inhibition of platelets activation, prodrug activation, binding to P2Y12 receptors and prevention of thrombus formation.[19]

Pakistan has wide diversity of ethnicities comprising of population from different backgrounds. The major ethnic groups in Pakistan are Punjabis, Sindhis, Pashtuns, Baloch, Kashmiri and Balti. The key enzyme involved in the conversion of clopidogrel to its active form is CYP2C19, a member of the cytochrome P450 enzyme family. Genetic polymorphisms in the CYP2C19 gene can lead to variability in the effectiveness of clopidogrel, as individuals with certain genetic variants may metabolize the drug more slowly or less efficiently.[20] Clinical efficacy of drugs used in treatment and prevention of ischemic heart diseases may differ among various ethnicities leading to formation of strategies regarding choice of drugs, dosing of drugs and duration of treatment in these ethnicities.[6,7] Studies have shown 16-65% of the patients on clopidogrel therapy have shown altered response to the drug, which is called as clopidogrel resistance.[8]

In this study, we tried to find out association between clopidogrel resistance and different ethnicities present in Pakistan.

MATERIAL & METHODS

It was a hospital based cross sectional study which included 390 patients from different ethnic origins of Pakistan. The study employed a non-probability purposive sampling method. The patients were divided into Punjabi, Pushtun, Sindhi, Baluchi, Kashmiri and Balti on the basis of their ethnicity. The study was conducted from 2015 to 2019 at Army Medical College, National University of Medical Sciences (NUMS), Pakistan. The study was granted ethical approval from the respective institution ref no ERC/SA-15/Dr. Usman Nawaz dated on 01 December 2015.

The patient from different ethnic origins were procured through non-probability purposive sampling from outpatient and inpatient cardiology departments of Armed Forces Institute of Cardiology (AFIC), NUMS. Inclusion criteria was Pakistani national ischemic heart disease patients of any age or gender taking clopidogrel 75mg/day for at least seven days. Exclusion criteria was non Pakistani nationals, lack of informed written consent, pregnancy, malignancy, hepatic or renal disease, use of tirofiban or eptifibatide within last 48 hours and omeprazole therapy.[9]

Blood sampling of all the patients was done after informed written consent. The blood was stored in plastic conical tubes containing sodium citrate as anticoagulant. Platelet rich plasma (PRP) and platelet poor plasma (PPP) were obtained by centrifuging the obtained blood. Chronolog light transmission aggregometer (Chrono-Log 490 Model, Chrono-Log Corporation, Havertown, Pennsylvania, USA) was used to assess platelet reactivity in PRP using ADP as an agonist and keeping PPP as reference.[10] The patients with platelet aggregation <50% were nominated as clopidogrel responders and ≥50% as clopidogrel resistant.[11,12]

Statistical Analysis

SPSS version 23 was used to analyze the obtained data. The gender, mean age, ethnicities, mean platelet aggregation and clopidogrel response status of the patients were expressed as numbers and percentages. Chi square test was applied to find difference in clopidogrel resistance among different ethnic groups. One way ANOVA and post hoc analysis were applied to assess the difference in mean platelet aggregation among different ethnic groups.

RESULTS

Demographic details of all the patients (n=390) from different ethnic origin of Pakistan are mentioned in Table-I.

Table-II is showing number and percentages of clopidogrel responders and clopidogrel resistant patients in various ethnic groups. Chi square analysis showed that there was no significant difference in prevalence of clopidogrel resistance among patients from various ethnic groups, $p = 0.566$.

		Punjabi (n=205)	Pushtun (n=71	Sindhi (n=30)	Baluchi (n=19)	Kashmiri (n=57)	Balti (n=8)
Gender (n)	Male	118	41	21	14	32	6
	Female	87	30	9	5	25	2
Age (years ± SD)	Mean	54.28±12.25	51.61±11.27	52.31±13.04	47.32±10.75	55.89±10.27	52.36±11.29
	Range	16 - 82	26 - 80	31 - 78	32 - 76	32 - 76	36 – 69

Table-I. Demographic details of patients from different ethnic origins

Ethnicity	Clopidogrel Responders n (%)	Clopidogrel Resistant n (%)	P-Value
Punjabi	153 (74.6%)	52 (25.4%)	0.566
Pushtun	59 (83.1%)	12 (16.9%)	
Sindhi	22 (73.3 %)	8 (26.7%)	
Baluchi	14 (73.7%)	5 (26.3%)	
Kashmiri	39 (68.4%)	18 (31.6%)	
Balti	6 (75%)	2 (25%)	

Table-II. Clopidogrel responders and resistant patients in different ethnic groups

Also, there was no significant difference in prevalence of clopidogrel resistance between male and female genders in all the groups (Punjabi p = 0.502, Pushtun p = 0.551, Sindhi p = 0.149, Baluchi p = 0.709, Kashmiri p = 0.952, Balti p = 346)

Figure-1 is showing mean platelet aggregation of patients on clopidogrel therapy in different ethnic groups on clopidogrel therapy. One way ANOVA and post hoc analysis revealed no significant difference in mean platelet aggregation among various ethnic groups, p = 0.330.

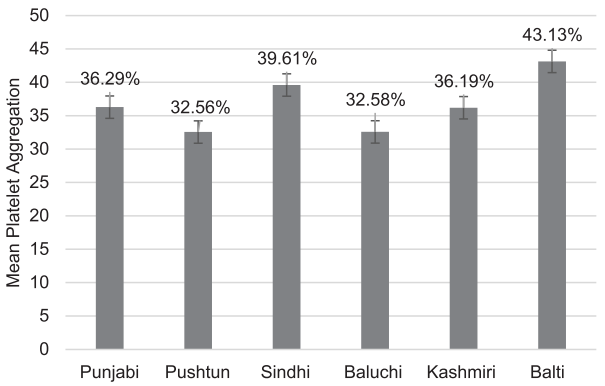

Figure-1. Mean platelet aggregation (%) of different ethnic groups

DISCUSSION

It is one of its kind studies in Pakistan to assess clopidogrel response among different ethnic groups on clopidogrel therapy. The results of current study shows that there was no difference in clopidogrel resistance among different ethnic groups of Pakistan, p = 0.566. However, prevalence of clopidogrel resistance was highest in Kashmiri patients (31.6%) and was lowest in Pashtun patients (16.9%). Punjabi (25.4%), Sindhi (26.7%), Baluchi (26.3) and Balti (25%) falls in intermediate range with respect to clopidogrel resistance.

Mean platelet aggregation of all the patients on clopidogrel therapy from different ethnic groups was also similar without any significant difference, p = 0.330. However, mean platelet aggregation of Balti group was highest 43.13±21.14% in relation to other groups. Mean platelet aggregation of Pashtun and Baluchi patients was lowest (32.56% and 32.58% respectively) among all the groups.

Studies have confirmed that clopidogrel response vary among individuals and different populations pertaining to different factors which may include CYP2C19 genetic polymorphism which affects clopidogrel metabolic activation inside body. As a result, active metabolites of clopidogrel are deficient in such individuals and antiplatelet action of clopidogrel is inefficient.[13,14] Ahmed et al. have demonstrated that clopidogrel resistance is related to haplotype (H1) of CYP2C19 gene and presence of diabetes mellitus in Pakistani cardiovascular patients on clopidogrel therapy.[12]

This study has shown that the prevalence of clopidogrel resistance is similar among various ethnicities present in Pakistan which shows that clopidogrel response is identical in all the ethnicities. Recent studies have shown that the response to clopidogrel, an antiplatelet medication, can exhibit significant variability among individuals. Some individuals may demonstrate a reduced response to the drug, referred to as hypo responders or non-responders. This variability in response has been associated with an increased risk of adverse cardiovascular events during follow-up. Reduced responsiveness to clopidogrel is frequently observed in Asian populations, a phenomenon primarily attributed to genetic polymorphisms linked with resistance to the drug. In certain Asian communities, this reduced responsiveness can be as high as 70%. From this information we can make an inference that dosing of clopidogrel should be similar in all patients regardless of their ethnicity.[15,16] However, interindividual variations within same ethnicity may be present due to any other factors like compliance, drug-drug interactions and difference in genetic makeup, which should be kept in mind and further explored if the drug does not show adequate antiplatelet response on therapeutic doses. Hence, it is crucial for healthcare providers attending to Asian patients to be mindful of the inter-individual differences in clopidogrel responsiveness when considering its prescription.[16]

CONCLUSION

There is no association between clopidogrel resistance and ethnicity in Pakistani population. This outcome challenges the assumption of a direct correlation between genetic background and clopidogrel responsiveness, highlighting the complex interplay of factors influencing drug efficacy. For future research endeavors in this field, there are several promising avenues to explore. First and foremost, a deeper investigation into the genetic markers and molecular mechanisms underlying clopidogrel resistance within the Pakistani population is warranted

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