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A Study of Role of Gender in High on Treatment Platelet Reactivity (HRPR) on outcome in Patients Undergoing Percutaneous Coronary Intervention

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Abstract

Background: Platelet inhibition is necessary in post PCI period as it is one of the risk factor for stent thrombosis and there are only few studies on platelet aggregation and inhibition for gender comparison between males and females.

Methods: We have studied 142 consecutive in patients from NIMS cardiology department from august 2014 to 2016 who underwent PTCA , in the follow up period of 15th day we did platelet aggregation test for all the patients . We calculated platelet inhibition by 100 – platelet aggregation.

Results: Out of 142 patients 30 are females 112 are males. Both the groups are matched in baseline characteristic of mean age 57 years, hypertension, diabetes, type of presentation (stable or unstable) weight, eGFR, type of stent, presence or absence of LV dysfunction, single or multi vessel disease. There is significant difference in smoking (p= 0.000) between males and females, and hemoglobin levels (12.12 v/s 13.60 g/dl, p = 0.04) but there is tendency for higher platelet aggregation (i.e. lesser platelet inhibition) in females, Chi square test person uncorrected chi square = 1.238, p=0.266, (fisher exact test 2 tailed p value 0.545) (Odds ratio (OR) = 0.00, 95% ci 0.00 to 6.649 Relative Risk (RR) = 0.00, 95% CI 0.00 TO 5.389). There are 9 (30%) females with higher end on platelet activity >50% in whom there are nil events in them and there are 24 (21.43%) males with higher end platelet activity >50% in whom there are 3 non cardiac events (AV fistula, CSA+CIN, CCF)in them but total event rate is higher in females(10%) than in males (8.04%). When estimate of difference is calculated with 95% CI is (-0.125) with test for difference 0 and p value of 0.064

Conclusion: Though there is a tendency of lesser platelet inhibition in female's events rates are higher compared to males (10% v/s 8.04%) with p = 0.064 which again shows tendency but not significance

Abbreviations:

HRPR	:	High on Treatment Platelet Reactivity
PCI	:	Percutaneous Coronary Intervention
PTCA	:	Percutaneous Transluminal Coronary Angioplasty
E GFR	:	Glomerular Filtration Rate
LV	:	Left Ventricular
Av fistula	:	Arterio Venous Fistula
CSA	:	Chronic Stable Angina
CIN	:	Contrast Induced Nephropathy
CCF	:	Congestive Heart Failure
ACS	:	Acute Coronary Syndrome
DAPT	:	Dual Antiplatelet Therapy
MACCE	:	Major Adverse Cardio and Cerebro Vascular Events
CAD	:	Coronary Artery Disease
CVA	:	Cerebrovascular Accident
MEHRANS	:	Bleeding Score
RBS	:	Random Blood Sugar
LFT	:	Liver Function Tests
KFT	:	Kidney Function Tests
ACC AHA	:	American College of Cardiology & American Heart Association
EDTA	:	Ethylene Diamine Tetraacetic Acid
LTA	:	Light Transmittance Aggregometry
PPP	:	Platelet Poor Plasma
SD	:	Standard Deviation

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Introduction

Coronary artery disease is one of the main causes of morbidity and mortality worldwide. Throughout the last decade improvements in the diagnosis and treatment of atherosclerosis have caused a marked reduction in the morbidity and mortality in men, whereas the rate of recurrent atherothrombotic events, including cardiovascular death, in women has increased .As platelet reactivity plays a vital role in thrombus formation and atherosclerosis, dual antiplatelet therapy with both aspirin and clopidogrel has become the cornerstone in the treatment of patients undergoing coronary stent implantation and those presenting with Acute Coronary Syndrome (ACS) .Previous studies have suggested that women do not accrue equal therapeutic benefit of antithrombotic therapy. Although multiple contributing factors have been described, the physiological mechanism behind this gender disparity remains unclear.

Gender differences in platelet function: Influence of gender on platelet biology was put forward over 30 years ago [1–4]. Sites of potential gender differences are in molecular mechanisms of platelet adhesion/aggregation. Latest works have shown that a gender and age difference in platelet count significantly (with higher values in women vs. men and in younger vs. older subjects), and that platelets in women have a higher number of surface receptors and to bind a greater amount of fibrinogen [5,3,6,7] .paradoxically females have higher bleeding tendency over males.

However, some are of opinion that platelet count and surface expression of glycoprotein (GP) Ib -IX-V (responsible for initiating adhesion through a von Will ebrand factor) and GP IIb/IIIa receptors (responsible for initiating aggregation mainly through fibrinogen) may not accurately reflect overall platelet reactivity [4].

Cardiovascular risk is still underestimated in women though they are experiencing higher mortality and worse prognosis after acute cardiovascular events. Cause of Acute coronary syndrome in females is plaque erosion as compared men where majority is due to plaque rupture which is nidus for platelet activation. Gender differences are seen in thrombotic and hemorrhagic risk during Dual Antiplatelet Therapy (DAPT), thus suggesting a potential variability in platelet reactivity according to sex.

Women are generally less represented than men in cardiovascular trials for reasons that include:

(i) Underestimation of cardiac risk due to atypical nature of angina, misinterpretation of symptoms, biased referral for cardiac testing, lower rates of appropriate diagnosis or treatment and lesser rates of referral to coronary angiography for acute coronary syndromes (ACS) [9].

(ii) Lower prevalence of cardiovascular diseases in women below the age of 65 .On the other hand, women included in antithrombotic drug trials are on average older and have more comorbidities and risk factors than men, and are thus at a higher risk of adverse outcomes, including thrombotic and bleeding events[10].

(iii) Moreover, because women are more prone to bleeding complications than men owing, to lower body weight, lower glomerular filtration rates, and more frequent overdosing of antithrombotic drugs, the net clinical benefit of antiplatelet agents tends to be generally smaller in women than in age-matched men[3-5]

Evidence that gender differences play a role in platelet reactivity was first reported over 30 years ago and this observation has been confirmed in many studies.

Compare the MACCE Between the Studies: Differences in vessel wall biology between men and women, as well as the direct influence of sex hormones (oestrogens, progesterone or androgens) on platelets or their indirect effect on the vasculature, might be underlying conditions from a biological point of view.

Since platelet reactivity plays a pivotal role in thrombus formation and atherosclerosis, dual antiplatelet therapy with both aspirin and clopidogrel has become the mainstay in the treatment of patients undergoing coronary stent implantation and those presenting with ACS. However, both drugs result in a wide interindividual range in platelet inhibition and the association between high end treatment platelet inhibition and the occurrence of adverse events is well established.

Therefore, the aim of the present study is to compare the magnitude of High on-Treatment Platelet Reactivity (HRPR) between genders in patients on dual antiplatelet therapy undergoing elective and emergency coronary stenting and their correlation with MACCE.

Aim & objectives

To see the affect of gender on platelet reactivity and there by complications associated with lower platelet inhibition.

Methods

Population and study design: This study was a retrospective, observational study including 142 patients with established coronary artery disease scheduled for elective and emergency coronary stent implantation.

Inclusion criteria: All patients with CAD who are undergoing stent implantation for elective and emergency indications from AUG 2014 to AUG 2015

Exclusion criteria:

1. Patients who have not given consent and who does not want to participate in the study
2. Who does not want platelet aggregation at 15 days of follow up
3. longevity less than 1year
4. high bleeding risk calculated using MEHRANS score
5. clinical or telephonic f/u not possible

Tests done

All routine blood examination profiles (RBS LFT KFT Lipid profile viral screen).In addition platelet aggregation test on day of procedure and 15th day post PCI.

In the present study all patients were on dual antiplatelet therapy with adequate clopidogrel treatment (defined as a maintenance dose of 75mg daily for > 5days, a loading dose of 600 mg at least 24h before PCI or 600 mg at least 4h prior to PCI) and low-dose aspirin of 80–100 mg daily for at least 10days.

The study was conducted according to the principles of the Declaration of NIMS. All patients gave written informed consent.

Clinical end point:

The clinical end point was a combination of all-cause death, non-fatal myocardial infarction(defined as the occurrence of ischaemic symptoms as well as a spontaneous troponin T value or creatine kinase MB greater than the upper limit of normal),definite stent thrombosis (according to the ACCAHA criteria) and ischaemic stroke any other cardio vascular events.

Blood sampling:

Prior to heparinisation, whole blood was drawn from the femoral or radial vein. Blood samples were collected into Vacutainer tubes containing 3.2% sodium citrate for all platelet function tests.

Blood samples for whole blood count were drawn into tubes containing K3-EDTA. Platelet function testing was performed within 2 h after blood withdrawal.

Platelet function testing

Light transmittance Aggregometry: Light Transmittance Aggregometry (LTA) was performed using an APACT 4004 Aggregometry (LABiTec, Arensburg, Germany) at 37°C.

Platelet poor plasma (PPP) was used as a reference for 100% aggregation and maximal platelet aggregation(%) was measured in non-adjusted platelet rich plasma after stimulation with arachidonic acid (AA) in a final concentration of0.5mg/ml to determine on-aspirin platelet reactivity and Adenosine Diphosphate (ADP) in a final concentration of 20 µmol/L to determine on- ANTIPLATELET DRUG platelet reactivity.

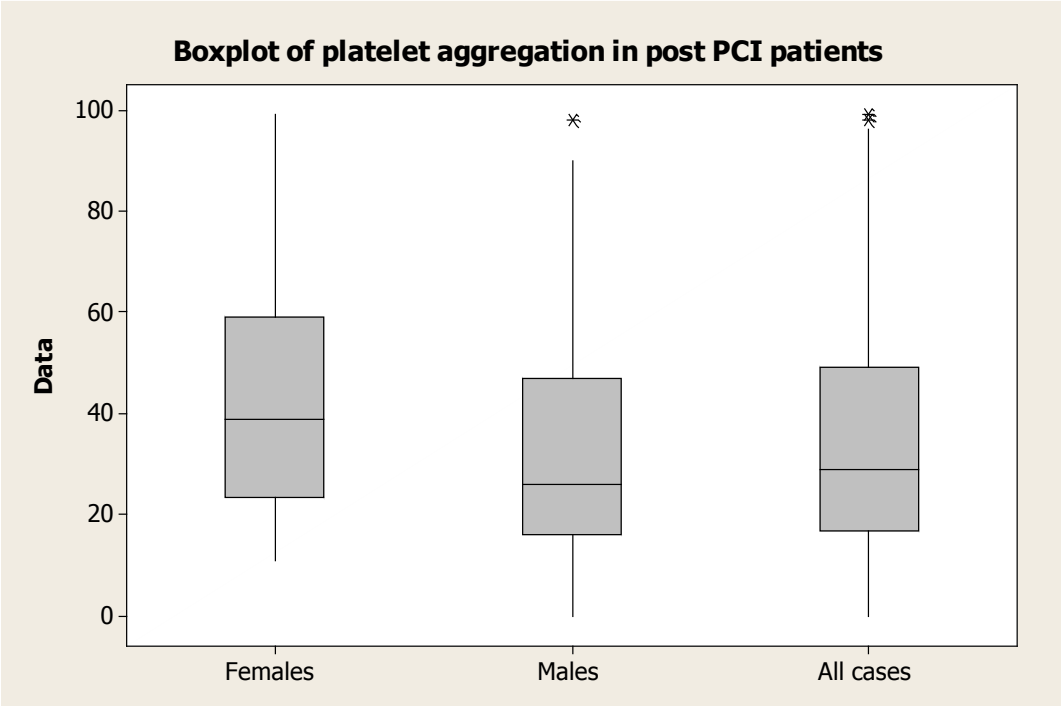

Figure 1: The box plot analysis shows that females have higher (HRPR) than males and over all cases. Follow up 15 days, 6mon, and 1yearTelephoneMacce end platelet inhibition Females 42.4+-24.3 Males 31.7+- 20.8P=0.017 statistically significant Higher end inhibition 30/21.43 tendency 2015 studies

Definition of high on treatment platelet reactivity (HRPR)

It is defined as > 50% platelet aggregation on ADP after pretreatment with asprin and clopidogrel and the analysis values are depicted in the (figure-1)

Statistical analysis

Continuous variables were expressed as mean ± SD, and categorical variables as frequencies (%). All distributions were checked for normality. Differences in continuous variables were compared by independent t-test and Dichotomous variables were compared by chi-square test

Results

A total of 142 patients who were admitted in our unit in the department of cardiology were included out of them 112(78.9%) males and 30(21.1%) were females with mean age of 57 years.

They were matched in baseline characteristics like age (mean age 57years) BMI (25kg/m^2) , hypertension, peripheral vascular disease, history of CVA , whether it is single or multi vessal disease, type of presentation and use of GP2b inhibitor during intervention these variables are given in table-1

But there is significant difference in smoking (p=0.00) and hemoglobin levels (p= 0.00) which were significantly higher in males and high number of diabetes (p < 0.01) in females and calculated CHADS2 VASC scores (p = 0.00) were higher in females (p = 0.00) that indicate females are sicker patients and more anemic compared to males as shown in table 2

LV dysfunction was more in males than females but statistically not significant.

Mean platelet aggregation in females on 15 day follow up is 42.43 with SD of 24.25 which is higher than males whose mean at 15 day follow up 31.72 with SD of 20.76 and higher than all cases 15 day follow up of 33.99 with SD of 21.89

The mean of total distribution 33.99. The distribution follows a bell curve which signifies there is normal Gaussian distribution.

Females 15 day follow up platelet aggregation has MODE of 49 where as males have a MODE of 19 and all cases have MODE of 25

This indicates females have higher platelet aggregation (HRPR) and lesser inhibition than males.

Discussion

Women often have been reported to exhibit a higher on treatment platelet reactivity for both on-aspirin and on-clopidogrel [2]. The results from the present study support previousfindings that women have higher end platelet reactivity and a higher magnitude of on-treatment platelet reactivity than men. In addition, the cut-offs to identify patients at higher risk of atherothrombotic events as well as the prevalence of the primary endpoint was similar between genders. Thus, thepresent study does not support the hypothesis that higher ontreatment platelet reactivity could account for the gender differences in clinical outcome and it remains highly questionable whether this gender-related difference in platelet reactivity has clinical relevance.

The study has established that patients exhibiting a high on-treatment end platelet inhibition > 50% status has NO higher tendencyforadverseeventspost-PCI which is in contrast to previous studies.

As platelet reactivity plays a vital role in thrombus formation and atherosclerosis, dual antiplatelet therapy with both aspirin and clopidogrel has become the cornerstone in the treatment of patients undergoing coronary stent implantation and those presenting with acute coronary syndrome (ACS) [13-14].

Conclusion

Though there is a tendency of high on treatment platelet reactivity(HRPR) in females,(10% v/s 8.04%) with p 0.064 compared to males this is not translated into the clinical events at one year even though females are sicker patients ,there is no correlation between MACCE and high on treatment platelet reactivity(HRPR). So there is no role for routine platelet aggregation test in uncomplicated PCI.

Parameter	Male	Female	p Value
Total No	112(78.9%)	30(21.1%)	-
Age	56.2 ± 10.4	57.1± 9.5	0.67
BMI	25.6 ± 4.9	25.2± 5	0.71
HTN	67 (59.8%)	22(73.3%)	0.15
GPI	9(8.04%)	4(13.3%)	0.43
PVD	2(1.8%)	0(0%)	0.15
CVA	2(1.8%)	0(0%)	0.15
Single/multiple vessel disease	69(61.6)	17(56.7)	0.6
ACS	60(53.6%)	16(53.3%)	0.98

Table 1: Base line Characteristic of Males and females

BMI = body mass index

HTN = hypertension GPI gp2b3a inhibitor

PVD=peripheral vascular disease

CVA = Cerebrovascular accident

ACS = Acute Coronary Syndrome

Parameter	Male	Female	p Value
Hemoglobin	13.534 ± 2.074	12.259 ± 1.405	0.000
Chads2 Vas Score	1.414 ± 1.311	2.700 ± 0.952	0.000
SM	45(39.3%)	1(3.33%)	0.000
LVD	49(43.8%)	8(26.7%)	0.067
DM	43(38.4%)	19(63.3%)	0.01

Table 2: Statistically significant parameters between males and females

SM = smoking
LVD= lv dysfunction
DM = diabetes mellitus

Discussion Future Scope

There is future scope for research as the evolution of newer antiplatelet drugs which have high bleeding tendency and females are more bleeding risk. Platelet aggregation POINT OF CARE test can also help solving this issue better

Limitations

1) We Have Included All Types Of Presentation But Sub Group Analysis Not Done and Only Concentrated On Gender

2) Single center study

Only followed for 1 year

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