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 multivessel 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
- 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 Willebrand 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 nidsus for platelet activation. Gender differences are seen in thrombotic and hemorrhagic risk during Dual Antiplatelet Therapy (DAFT), 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 1 year
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 > 5 days, a loading dose of 600 mg at least 24h before PCI or 600 mg at least 4h prior to PCI) and low-dose a aspirin of 80–100 mg daily for at least 10 days.

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 ACC/AHA 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, Arentsberg, 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 of 0.5mg/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
Females 15 day follow up platelet aggregation has MODE of 49 whereas 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 previous findings 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, the present study does not support the hypothesis that higher on-treatment 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 tendency for adverse events post-PCI which is in contrast to previous studies.

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.
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

References

Table 1: Base line Characteristic of Males and females

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

Table 2: Statistically significant parameters between males and females

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

SM = smoking
LVD = LV dysfunction
DM = diabetes mellitus

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 |

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