ORIGINAL ARTICLE

Effectiveness of Ranolazine to Prevent Myocardial Injury During Elective Percutaneous Coronary Intervention

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ABSTRACT

Background: Ranolazine is a novel antianginal drug that reduces intracellular accumulation of calcium ion in ischemic myocardium. A pilot randomized study (n=70) has shown that pretreatment with ranolazine 1000mg twice daily for 7days significantly reduced periprocedural myocardial injury (PMI) in elective Percutaneous coronary intervention (PCI). Our objective was to detect whether similar effect could be obtained by ranolazine pretreatment through an interventional study.

Materials & Methods: 110 patients with chronic stable angina scheduled for elective PCI were enrolled in an interventional study. For 7 days before the procedure, 55 patients were allocated to receive ranolazine 1000 mg twice daily (ranolazine group) and 55 patients didn't receive ranolazine (control group). Serum creatinine kinase-MB (CK-MB) and Troponin I levels were measured at baseline and 24 hours post procedure.

Results: Periprocedural myocardial injury [i.e. an elevation of serum biomarkers (preferably cardiac troponins) above the 99th percentile of upper reference limit (URL)] was detected less commonly after PCI in ranolazine than in control group (11% vs. 27%, p=0.0001). Also, PCI-related myocardial infarction [i.e., post procedural increase in CK-MB>3 times above the URL] tended to be lower in the ranolazine versus placebo group: 1.8% versus 5.45%, P=0.0002. 24 hours post procedural levels of cardiac markers were also significantly lower in the ranolazine versus control group (CK-MB: 2.42±2.05 versus 7.02±9 ng/ml, P=0.001; Troponin 1: 0.447±0.74 versus 1.18±1.6 ng/ml, P=0.004). No significant adverse effect of the drug was reported.

Conclusion: So, we have concluded that ranolazine was effective in significantly reducing the periprocedural myocardial injury in elective PCI.

Key Words: Ranolazine, Periprocedural Myocardial Injury, Elective Percutaneous Coronary Intervention.

Introduction

Coronary artery disease (CAD) is now the most common cause of death worldwide; it is on the rise and has become a true pandemic that respects no borders.[1] According to the Global Burden of Disease Study[2], the developing countries contributed 3.5 million of the 6.2 million global deaths for CAD in 1990. The projections estimate that these countries will account for 7.8 million of the 11.1 million deaths due to CAD in 2020. In 2005, CAD caused approximately 1 of every 5 deaths in the USA.[3]

Bangladeshi people, like other south Asians, have high susceptibility to ischemic heart disease (IHD) but population-based data are lacking in Bangladesh.

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A prevalence of 3.4% was recorded in rural population with traditional lifestyle and thin body mass index.[4]

Bhopal R et al in a cross sectional study[5] among the south Asian people in United Kingdom showed that for most risk factors, the Bangladeshis (particularly men) fared the worst: smoking was most common (57%) in them and Bangladeshis had the highest concentrations of triglycerides (2.04 mmol/L) and fasting blood glucose (6.6 mmol/L) and the lowest concentration of high density lipoprotein cholesterol (0.97 mmol/L).

The treatment of CAD has evolved considerably over the past decades. Along with lifestyle modification and pharmacological treatment, percutaneous coronary intervention (PCI) has become a standard revascularization procedure for patients with CAD. Since the first description of coronary angioplasty in man by Andreas Gruntzig in 1977, the procedure has been extensively modified[6]. About one-third of all elective PCI procedures are associated with significant myocardial injury, termed peri-procedural myocardial injury (PMI), which has been associated with increased subsequent mortality[7].

The most common (50-75%) mechanisms of myocardial injury during PCI are distal embolization and side branch occlusion (SBO)[6]. Other significant causes include dissection, thrombus, no reflow or slow flow; or coronary perforation[6].

Cardiac biomarkers have been extensively used in the past two decades to establish the incidence and the prognostic implication of PMI[6]. Several meta-analyses have inferred the proportionate increase in the early and late mortality with increased creatinine phosphokinase MB isoenzyme (CK-MB) and Troponin release periprocedurally[7,8,9,10].

Currently, there are some pharmacologic agents to combat PMI6eg, antiplatelets, antithrombotic, statins, beta blockers, adenosine, trimetazidine etc. But PMI still remains the most frequent complication of PCI occurring in 5-30% of patients[11]. So, new adjunctive therapy is needed for better tackling PMI.

Ranolazine is a new antianginal drug that was approved on January 27, 2006 in the United States for use in patients with chronic stable angina who continue to be symptomatic on β blockers, calcium antagonists or nitrates[12]. Ranolazine has the potential to partially disrupt the consequences of cell hypoxia during transient myocardial ischemia by reducing excess late sodium ion influx; thereby reducing intracellular calcium overload. The efficacy and safety of ranolazine in ischemic heart disease is well established in different randomized clinical trials.[13,14,15,16]

A recently completed Randomized, double-blind, placebo-controlled pilot study has shown that pretreatment with ranolazine l000 mg twice daily for 7 days significantly reduced procedural myocardial injury in elective PCI[17]. However, no such study has yet been done in Bangladesh. As the socio demographic factors, ethnicity and physical factors of patients in Bangladesh are different from the patients of European origin, we carried out such a study in our institute. In this study we have verified whether pretreatment with Ranolazine before elective PCI has any protective effect against PMI.

Materials & Methods

110 patients with chronic stable angina scheduled for elective PCI at University Cardiac Center, BSMMU from June 2012 to February 2013, who fulfilled the eligibility criteria were enrolled in a prospective, single center, interventional study.

Eligibility Criteria

i) Inclusion criteria -

- Angiographically proven significant coronary artery disease.
- Class I indication for elective PCI,

ii) Exclusion Criteria:

- Acute coronary syndromes (unstable angina or myocardial infarction) within 3 months.
- Any increase in baseline values of markers of myocardial damage (Troponin I and creatinine kinase-MB)
- Renal failure with estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2.

- An increase in liver enzymes, especially SGPT, more than twice the upper reference limit.
- Left ventricular ejection fraction $<40\%$.
- Prolongation of corrected QT interval in the baseline ECG (>0.45 sec for males & $>$ 0.46 sec in females).
- Patients taking drugs known to prolong QT interval, e.g. Class Ia & Class III anti-arrhythmic drugs, tricyclic antidepressant drugs, phenothiazines, macrolides etc[18].
- Patients taking drugs that are moderately potent cytochrome P450 3A4 enzyme inhibitors[12], e.g. ketoconazole, paroxetine, diltiazem, verapamil, macrolides, HIV protease inhibitors and grape fruit juice.
- Patients who had been taking ranolazine before enrollment.
- History of chronic liver disease or muscle disease.

The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of our institution (Registration number: BSMMU/2012/05 87). The sample size was calculated at 5% level of significance and 90% power using a relevant formula.[19,20] For 7 days before the procedure, 55 patients were allocated to receive Ranolazine 1000 mg twice daily (Ranolazine group) and 55 patients didn't receive Ranolazine (control group). The baseline characteristics of the patients of both Ranolazine and control group (Age; Gender; BMI; Risk factors for atherosclerosis: DM, HTN, dyslipidemia, current smoking; coronary angiographic diagnosis and characteristics of coronary artery lesions) were well-balanced prior to allocation. All patients in both group were pretreated with oral aspirin (75 mg/day) and had a loading dose of Clopidogrel 600 mg before the procedure. Other medications such as (β-blockers, calcium antagonists, statins and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) were given as appropriate. During enrollment, ECG was performed and blood samples were taken before PCI to analyze baseline Troponin I and CK-MB values at the same laboratory. Angiographic analysis was performed with a computer-assisted automated edge-detection system (SIEMENS AXIOM, Germany). During PCI, all patients were given a 60 IU/kg intravenous bolus of unfractionated heparin. Stents were deployed in femoral arterial route according to current practice guidelines and any complication occurring during PCI was noted. Glycoprotein IIb/IIIa inhibitors and nitrates were administered according to the operator's discretions. Blood samples were taken at 24 hours after PCI for measurement of CK-MB and Troponin I using standard laboratory method.[21,22] Standard 12-lead electrocardiograms were recorded in all patients before PCI, at the end of PCI, and at 24 hours after PCI. Any symptom occurring within the first 72 hours after PCI (i.e. during hospital stay) was recorded. All patient received Clopidogrel 75 mg/day for at least 1 month in addition to continued aspirin (75mg/day) after PCI. Data were collected using a structured questionnaire containing the key variables of interest. Variables were defined by standard operational definitions.[2,4,23-29] Parametric data were compared between two groups by Student's t test and categorical data were compared between two groups by Chi Square test or Fisher's exact test. The primary end point was the occurrence of periprocedural myocardial injury (PMI) i.e., an elevation of serum biomarkers (preferably cardiac troponins) above 99 thpercentile of upper reference limit after PCI assuming a normal baseline troponin value.The secondary end point was the occurrence of PCI-related myocardial infarction i.e., an elevation of serum cardiac biomarkers to more than three times the 99th percentile of URL. The composite end point of the analysis was the incidence of Major Adverse Cardiac Events (MACE) defined as death, spontaneous myocardial infarction (MI), target vessel revascularization (TVR) or stroke, by 30 days of PCI.

Results

Among 132 patients admitted for elective PCI with a diagnosis of chronic stable angina, 110 patients were ultimately eligible for our study. The enrolled participants were allocated to Ranolazine group

(n=55) and control group (n=55). The baseline characteristics and angiographic characteristics were well-balanced between the two groups. The procedural characteristics (use of direct stenting, maximum pressure inflation and use of post-dilatation), number of drug-eluting stents, stent diameter and the length of stents were similar in both the groups. Stents were deployed in all patients and angiographic success was achieved in all of them. The occurrence of procedural complications was similar in both the groups. Periprocedural myocardial injury [i.e. an elevation of serum biomarkers (preferably cardiac troponins) above the 99th percentile of upper reference limit (URL)] was detected less commonly after PCI in Ranolazine than in control group (11% vs. 27%, p=0.0001). Also, PCI-related myocardial infarction [i.e., post procedural increase in CK-MB>3 times above the URL] tended to be lower in the Ranolazine versus placebo group: 1.8% versus 5.45%, P=0.0002. 24 hours post procedural levels of cardiac markers were also significantly lower in the Ranolazine versus control group (CK-MB: 2.42 ± 2.05 versus 7.02±9 ng/ml, P=0.001; Troponin 1: 0.447±0.74 versus 1.18±1.6 ng/ml, P=0.004). No significant adverse effect of the drug was reported. There were no in-hospital and 30-day Major Adverse Cardiac Events (cardiac death, spontaneous MI, target vessel revascularization and stroke) in any of the groups.

Table-1: Preprocedural medications and baseline investigations in the two groups (n=l10):

Variables Case	(n==55)	Control (n=55)	p value
Medications			
Aspirin, n(%)	55(100)	55(100)	1.000
Clopidogrel loading n(%)	55(100)	55(100)	1.000
Statins, n(%)	55(100)	55(100)	1.000
Beta Blockers, n(%)	47(85.45)	50(90.9)	0.313
ACEI/ARB,n(%)	31(56.4)	30(54.5)	0.967
Nitrates, n(%)	51(92.7)	53(96.4)	0.687
Investigations before enrollment			
S. creatinine (mg/dl)	0.91±0.3	0.91±0.2	0.317
SGPT (IU/L)	21±10	21±19	0.898
WBC Total count (U/L)	6931±1820	6647±1950	0.446

Table-1 shows that the percentage of patients receiving Antiplatelets, statins, beta blockers, ACEI/ ARB and nitrates were similar in both the groups

Table-2: General Characteristics of the patients enrolled in the two groups (n=110):

Variables	Case (n=55)	Control (n=55)	p value
Age (years)	49±5	50±7	0.481
Male, n(%) ("render	41(74.5)	43(78.2)	0.447
Female, n(%)	15(25.5)	12(21.8)	0.447
BMI (kg/m2)	25±2	25±3	0.368
Hypertension, n(%)	38(69.1)	40(72.7)	0.812
Current Smokers, n(%)	18(32.7)	21(38.2)	0.940
Diabetes, n(%)	17(30.9)	16(29.1)	0.972
Dyslipidemia, n(%)	23(41.8)	20(36.4)	0.438
Family History of IHD, n(%)	7(12.7)	8(14.5)	0.983
Previous Stroke, n(%)j	0	0	
Previous Myocardial Infarction, n(%)	5	4	0.653
Previous Coronary Intervention, n(%)	0	0	
Left Ventricular Ejection Fraction, (%)	57±6	58±5	0.976

Table-2 shows both ranolazine and control groups were similar with regard to their demographic and clinical characteristics.

Table-3: Distribution of patients based on increase in Post procedural cardiac biomarker level (n=l 10).

CK-MB	Case(n=55)	Control(n=55)	p value
No increase, n(%)	49(89.1)	40(72.72)	0.0002
Any elevation above URL, n(%)	5(9.1)	12(21.83)	0.0002
Elevation >3-time, n(%)	1(1.8)	3(5.45)	0.0002.
24 hours after PCI (ng/ml)	2.42±2.05	7.02±9	0.001
Troponin I			
No increase, n(%)	48(87.27)	37(67.27)	0.0001
Any elevation above URL, n(%)	6(11)	15(27.27)	0.0001
Elevation >3-time, n(%)	1(1.8)	3(5.45)	0.0001
24 hours after PCI (ng/ml)	0.447±0.74	1.18±1.6	0.004

Table-3 shows that periprocedural myocardial injury was detected in fewer patients in the Ranolazine group

than in control group. There were less patients in the Ranolazine than in control group with increases in CK-MB level above the URL. Overall, PCI-related myocardial infarction occurred in fewer patients in the Ranolazine group versus the control group. Mean pre-procedural levels of the 2 markers were similar and were within the normal limit in the 2 groups. However, the values obtained 24 hours post-PCI were significantly lower in Ranolazine group than those in control group.

Discussion

This study demonstrates that pretreatment with Ranolazine 1000 mg twice daily for 7 days significantly reduced periprocedural myocardial injury (11% versus 27.27%, P=0.0001) and PCI-related myocardial infarction (1.8% versus 5.45%, P=0.0002) during elective PCI the results of our investigation support the hypothesis that Ranolazine may offer protection to cardiac myocyte from ischemic injury during PCI. Ranolazine has a unique mechanism of action because it prevents the increase in intracellular calcium concentration in ischemic myocardium. Our finding is consistent with the first pilot, randomized trial[17] which demonstrated that pretreatment with Ranolazine is effective in decreasing the incidence of myocardial injury during PCI. Indeed, Ranolazine significantly reduced release of all markers of myocardial damage after PCI, including CK-MB and Troponin-I. No significant side effect of Ranolazine was reported during this study and QTc was not found to be prolonged after treatment with Ranolazine. So, Ranolazine was found to be safe in this study as was found in previous studies.[13,14,15,16]

However, the incidence of periprocedural myocardial injury and PCI-related myocardial infarction in both groups were lower than that observed in the pilot study[17]. In the pilot study, PMI was observed in 23% of patients in Ranolazine group and 40% of patients in control group, whereas PCI-related myocardial infarction occurred in 6% patients in Ranolazine group and 22% of patients in control group. This low incidence in our study can be explained by the discrepancies of several factors which have major implications in the incidence of PMI. First, the mean age of patients in our study (49 years in Ranolazine and 50 years in control group) was lower than that in the pilot study (64 years in Ranolazine and 60 years in control group). Second, the number of cases where the LAD was intervened was lower in our study (50% in Ranolazine and 48% in control group) compared to the previous study (69% in Ranolazine and 57% in control group). Third, the number of stents deployed per patient was lower in this study (1.6 in Ranolazine and 1.46 in control group) than that in the pilot study (1.95 for Ranolazine and 1.75 in control group). Fourth, post-dilatation was done in fewer cases in our study (6.8% in Ranolazine and 8.4% in control group) compared to the cases in the pilot study (69% in Ranolazine and 71% in control group). The use of fewer post-dilatation has reduced the total ischemic time and might have contributed to the lower incidence of PMI in our study. Fifth, intervention of bifurcation lesion with kissing balloon was done in the pilot study in 26% of cases in Ranolazine group and 20% cases in the control group. But, this complex technique was not applied in any patient of our study. Lastly, there might have been some ethnic and genetic variation in the susceptibility to PMI in our patients compared to the European patients. We found no major adverse cardiac event (MACE) during the in-hospital and after one month in any of the groups.

Conclusion

Percutaneous coronary intervention (PCI) is a well-established and relatively safe procedure for the treatment of chronic stable angina. However, periprocedural myocardial injury (PMI) is common after PCI and has an important impact on long-term prognosis. PMI complicating PCI has not received as much emphasis as other aspects of PCI. So, the patients of chronic stable angina who are scheduled for elective PCI deserve an intensive application of preventive measures to be protected from PMI. Different treatments are available to prevent myocardial injury during elective PCI. Nevertheless, the incidence of PMI is high. So, adjunctive therapy for further protection of the myocardium from ischemic insult at the time of PCI is still needed. Ranolazine is a safe & effective oral medication which was shown to be effective in reducing PMI during elective PCI. So, this novel pharmacological agent offer hope in further reduction of the incidence of PMI.

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Conflict of Interest: None.

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