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Original Research Paper

Cardiology

A STUDY TO ASSESS THE EFFECT OF TRIMETAZIDINE ON MICROVASCULAR FLOW IN PATIENTS OF ACUTE MYOCARDIAL INFARCTION UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

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ABSTRACT

Background: Trimetazidine is an anti-anginal drug that shifts substrate utilization from fatty acid to carbohydrates, thereby, increasing myocardial glucose oxidation and improving myocardial ischemia. It has also been found to be effective in limiting the peri procedural myocardial injury in patients of chronic coronary syndrome undergoing Percutaneous coronary intervention (PCI). The aim of this study was to assess the effect of Trimetazidine on the microvascular flow achieved in the affected artery post PCI in patients of Acute Myocardial Infarction (AMI). **Material and Methods:** In this observational comparative study at Medical College and Hospital, Kolkata, 40 patients with AMI were assigned randomly into two groups, one group with trimetazidine added to standard therapy (n= 19) and another group with standard background therapy without trimetazidine (n=21), during the period September 2021 – August 2022.Cardiac Troponin I (cTnI) and Creatine Phosphokinase MB (CKMB) were measured before and 48 hrs after PCI, ST segment changes on ECG were assessed, Ejection fraction on 2D Echo was measured before PCI and 1 month after PCI, post PCI coronary blood flow was assessed by TIMI Frame Count and recurrence of angina post PCI was measured in the two groups. **Findings:** The patients of the two groups were matched for their ages, gender, type of MI and comorbidities. There was no significant difference in the level of TnI and CKMB in the two groups post PCI. After PCI ST segment resolution on ECG was significantly higher in Trimetazidine group (68.4%) as compared to non- Trimetazidine group (28.6%) ($Z=5.51;p<0.0001$).There was no significant difference in pre PCI and post PCI Ejection fraction in the two groups. Abnormal TIMI Frame count was significantly higher in Non-trimetazidine group (52.4%) than Trimetazidine group (21.1%) ($Z=4.55;p<0.0001$).Recurrence of angina was significantly lower in Trimetazidine group (94.7%) than non-Trimetazidine group (61.9%) ($Z=5.68;p<0.01$). **Conclusion:** This study showed that trimetazidine improves microvascular coronary flow in the patients of AMI undergoing PCI and leads to significant resolution of ST-T changes on ECG with significant relief from angina. Larger studies are therefore required in this regard for trimetazidine to be recommended for improvement of coronary microvascular flow in patients of AMI undergoing PCI.

KEYWORDS :

INTRODUCTION:

Acute myocardial infarction(AMI) remains as major cause of cardiovascular morbidity and mortality worldwide [1]. Percutaneous coronary intervention is an important treatment strategy for management of patients of AMI. With various technical advancement incidence of major complications during PCI like acute myocardial infarction, urgent coronary artery bypass graft surgery or death has reduced significantly[2,3].However, the PCI may induce coronary spasm or endothelial cell injury, distal embolization of debris from atherosclerotic plaque, thereby leading to myocardial ischemia or myocardial injury[4,5]. Minor peri/post-procedural myocardial injury or necrosis plays a crucial prognostic role after PCI[6].Anti anginal drug, Trimetazidine acts by selectively inhibiting long-chain 3-ketoacyl-CoA thiolase and directly stimulating pyruvate dehydrogenase thereby shifting cardiac energy metabolism from fatty acid oxidation to glucose oxidation, which can preserve the necessary ATP level in myocardial cells under hypoxic conditions, promote a decline in intracellular acidosis, and protect cardiac myocytes from calcium overload[7].

It can thus limit the myocardial injury and improve myocardial function[8,9].Trimetazidine has been found experimentally to inhibit coronary microembolization and myocardial apoptosis leading to a cardioprotective effect.[10,11]

India has one of the largest burden of Coronary Artery Disease (CAD) in the world. Symptoms of CAD arise a full 10 years earlier in Indian population than in western countries. Premature CAD in young Asian Indians could be partly explained by increased vascular inflammation[12]. Trimetazidine significantly suppresses the inflammatory markers in patients undergoing PCI [13]. Considering the role of vascular inflammation in Indian population, Trimetazidine can improve the outcome in AMI patients undergoing PCI.

SUBJECTS AND METHODS:

This observational comparative study was conducted at the Department of Cardiology, Medical College and Hospital, Kolkata, between September 2021 and August 2022.Study protocol was approved by Institutional Ethics Committee. The study procedure was in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient prior to the study enrolment.

Patients

Patients admitted with Acute Myocardial Infarction (AMI)

undergoing urgent Percutaneous Coronary intervention (PCI) in Department of cardiology, Medical College and Hospital during the study period were assigned randomly into two groups before PCI, one group with trimetazidine (35mg BD) added to standard therapy and another group with standard background therapy without trimetazidine.

The patients more than 18 years of age, undergoing urgent PCI for AMI (non-ST elevation MI and ST elevation MI) and giving consent for study were included. Patients having deranged renal function tests, liver function test or overwhelming sepsis, in cardiogenic shock or having unstable arrythmias, patients of Acute Coronary Syndrome (ACS) undergoing CABG or continuing optimal medical therapy, patients of Unstable Angina and Pregnant patients were excluded from the study.

Standard medical therapy in both the groups included Dual Antiplatelet, Statin, ACE inhibitor, Heparin nitrate and beta blocker. Patients in trimetazidine group received trimetazidine 35mg BD on the day of admission and was continued till 2 months after PCI. Baseline investigations including complete hemogram, renal and liver function tests, lipid profile and blood sugar were done in both the groups. All enrolled patients underwent coronary angiography and subsequent angioplasty as per institutional protocol with drug eluting stents. Levels of cardiac biomarkers i.e. Troponin I (cTnI) and Creatine Phosphokinase MB (CKMB) were measured before and 48 hrs after PCI (with 99th percentile URL of 19ng/L for cTnI and 25 IU/l for CKMB), ST segment changes on ECG were assessed, Ejection fraction on 2D Echo was measured before PCI and 1 month after PCI, post PCI coronary blood flow was assessed by TIMI Frame Count and recurrence of angina post PCI was measured in the two groups.

Statistical Analysis

Statistical Analysis was performed with help of Epi Info (TM) 7.2.2.2 EPI INFO is a trademark of the Centers for Disease Control and Prevention (CDC). Descriptive statistical analysis was performed to calculate the means with corresponding standard deviations (s.d.). Test of proportion was used to find the Standard Normal Deviate (Z) to compare the difference proportions and Chi-square ( ) test was performed to find the associations. t-test was used to compare the means of the two groups. $p<0.05$ was taken to be statistically significant.

RESULTS

A total of 40 patients of ACS were included in this study out of which 19(47.5%) and 21(52.5%) were in Trimetazidine and non- Trimetazidine group respectively.

Demographic characteristics matched in both the groups. Mean age was 52.42years and 55.05years in trimetazidine and non- trimetazidine group respectively. Both the groups matched for their gender. Co-morbidities like DM, HTN , CAD and habit of smoking were more or less equally distributed over the patients of the two groups. Patients of the two groups were comparable for type of MI. Both the groups were also comparable with regard to use of cardiac medications including antiplatelet drugs, statins, -receptor blockers, ACEI, and nitrates.

Angiographic characteristics

Number of coronary arteries involved, number and type of stents deployed, mean inflation pressure and mean inflation time were more or less equally distributed in both the groups. 63.2% patients had single vessel coronary artery disease (SV-CAD), 31.6% had Double vessel CAD (DV-CAD) and 5.3% had Triple vessel CAD (TV-CAD) in the Trimetazidine group, while 61.9% patients had SV-CAD, 33.3% had DV-CAD and 4.8% had TV-CAD in the non- trimetazidine group($p=0.99$). In Overall distribution of the angiographic lesions 52.5% had type B2 lesion followed by 47.5% of type A lesions. Type B1 lesion was significantly higher in non- Trimetazidine group (38.1%) as compared to Trimetazidine group (15.8%) ($Z=3.50; p<0.0001$). Mean no. of stents deployed per patient was comparable between the two groups. Mean inflation time was 10.74 seconds and 12.86 seconds in the trimetazidine and non-trimetazidine groups respectively. Mean maximal inflation pressure was 15.47mmHG and 16 mmHg in the trimetazidine and non-trimetazidine groups respectively.

Table-1 showing baseline demography and angiographical charactersistics in the two groups. Anterior wall myocardial infarction(AWMI),inferior wall myocardial infarction(IWMI)

DEMOGRAPHY			
VARIABLE	Trimetazidine group (n=19)	Non Trimetazidine group (n=21)	P value
Age (in years)	52.42	55.05	0.368
Gender	15 (M) 4 (F)	16(M) 5(F)	0.83
Diabetes	11	6	0.06
Hypertension	10	10	0.751
Smoking	12	14	0.81
MI AWMI IWMI NSTEMI	 9 7 3	 13 6 2	0.21
ANGIOGRAPHY CHARACTERSISTICS			
Number of arteries involved Single Double Triple	 12 6 1	 13 7 1	0.99
Type of lesion A B1 B2 C	 10 3 10 3	 9 8 11 2	 0.15 0.04 0.99 0.54
Number of stent	1.21	1.23	0.86
Total inflation time	10.74	12.86	0.329
Max inflation pressure	15.471	16	0.580

Effect of cardiac biomarkers: Preoperative Cardiac Troponin I and CKMB levels were comparable in the two groups and there was no significant difference in the level of cardiac troponin I and CKMB 48 hours post PCI in the two groups

Table- 2 showing levels of biomarkers viz. cTnI and CKMB preoperatively and 48hours post operatively in the two groups

Parameters	Group	Mean	s.d.	t-value	p-value
Pre-operative TROP-I	Trimetazidine	111.32	27.47	1.802	0.080 NS
	Non-trimetazidine	95.76	27.02		
TROP-I Post-operative 48 hours	Trimetazidine	38.95	30.39	1.088	0.283 NS
	Non-trimetazidine	50.57	37.08		
Pre-operative CKMB	Trimetazidine	204.95	165.16	1.086	0.289 NS
	Non-trimetazidine	160.86	66.90		

CKMB Post-operative 48 hours	Trimetazidine	64.63	40.52	0.616	0.542 NS
	Non-trimetazidine	75.29	66.83		

The findings of ECG with respect to ST elevation before PCI were equally distributed in the two groups. However, significant difference was found after PCI (p=0.011). After PCI proportion of patients with decrease in ST elevation on ECG was significantly higher in Trimetazidine group (68.4%) as compared to non- Trimetazidine group (28.6%) (Z=5.51; p<0.0001).

Pre-operative and post-operative EF were equal among the patients of the two groups. However, patients with post-operative EF>50% was higher in Non-trimetazidine group (15.4%) than Trimetazidine group (11.8%) but it was not significant (Z=0.62;p=0.53).

Abnormal TIMI Frame count was significantly higher in Non-trimetazidine group (52.4%) than Trimetazidine group (21.1%) (Z=4.55; p<0.0001).

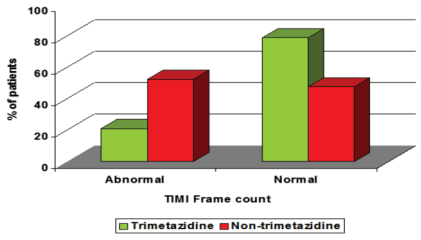

Figure1- Comparison of TIMI frame count post PCI in the two groups showing significant improvement in the trimetazidine group.

Patients with no post procedural complication was higher in Trimetazidine group (89.2%) than non-Trimetazidine group (76.2%) but it was not significant (Z=2.41;p=0.015). Post PCI angina was significantly more in the non- trimetazidine group (38.3%) as compared to the trimetazidine group (5.3%) (Z=5.68;p<0.01).

DISCUSSION:

Polonski et al reported that patients of stable angina undergoing PCI receiving trimetazidine 60mg 4 days before PCI showed reduction in angina, rhythm disturbances, and ischemic ST-T changes, however there was nonsignificant trend to lower levels of cTnI at 6 and 12 h after the PCI.[14] However a study by Bonello et al showed significant decrease in the levels of cTnI in the patients of stable angina undergoing PCI administered 60mg loading dose of Trimetazidine before PCI.[15] Xu et al also showed that patients of unstable angina undergoing PCI had significant lower troponin levels post PCI in the trimetazidine group.[16] Chen et al found that pre PCI administration of Trimetazidine significantly reduced the angina, ST-T changes and improved the ejection fraction.[17] In a meta-analysis of nine randomized trials of 778 patients undergoing PCI, Zhang et al reported that periprocedural administration of TMZ not only significantly improved LVEF but also reduced elevation in cTnI level, angina episodes during PCI, and ischemic ST-T changes on the ECG during PCI.[18]. A study by Steg PG et al found that use of intravenous Trimetazidine as adjunctive to other therapy was safe and led to earlier resolution of ST-segment elevation in patients treated by primary angioplasty for acute myocardial infarction[19].Another study by Labrou et al[2] showed the beneficial effect of trimetazidine on biomarker release pattern and echocardiographic LV function after PCI in patients with ACS. However, the ATPCI trial in efficacy and safety of Trimetazidine after PCI showed no significant differences with respect to the primary end points of cardiac death, hospital admission for cardiac event, angina leading to CAG, angina leading to increase in ant - anginal therapy.[20] In our study we found that Preoperative Cardiac Troponin I and CKMB levels were comparable in the two groups and there was no significant difference in the level of cardiac troponin I and CKMB 48 hours post PCI in the two groups. Most of the patients in both the groups demonstrated a decrease in level of biomarkers post PCI except 19% patients in non-trimetazidine group showed an increase of post PCI troponin I whereas 15.7% patients in trimetazidine group showed the increase in post PCI troponin I (not significant). Similarly, 14.2% patients in non-trimetazidine group showed an increase in post PCI CKMB while 10.5% in trimetazidine showed an increase in post PCI CKMB (non-significant). All patients who demonstrated post-PCI rise in cTnI had a "myocardial injury" and not Type 4a PCI-related myocardial infarction because there was no evidence of ischemic symptoms or MI on ECG, angiographic, or imaging findings in any of the patients. Both the groups were comparable in the distribution of ST elevation MI with non-significant differences in findings of ECG of the patients of the two groups before and during PCI (p>0.05). However, significant difference was found after PCI (p=0.011). After PCI proportion of patients with ST segment resolution on ECG was significantly higher in Trimetazidine group (68.4%) as compared to non-Trimetazidine group (28.6%) (Z=5.51;p<0.0001). 42 % patients in the trimetazidine group demonstrated an increase in ejection fraction measured by 2D ECHO 1 month post PCI whereas 33% in non-trimetazidine group demonstrated the increase in EF, however these differences were not significant.
In this study we also found that there were no significant differences in type of MI and the number of arteries involved angiographically between the two groups. Angiographic distribution of lesions was characterized by type B1 significantly higher in non- Trimetazidine group (38.1%) as compared to Trimetazidine group (15.8%) (Z=3.50; p<0.0001).Overall B2 (52.5%) followed by A(47.5%) were significantly higher than other lesions (Z=2.91; p=0.0003). Both the groups matched in respect to the number of stents deployed per person, mean maximal inflation pressure and inflation time. It was found that the Abnormal TIMI Frame count was significantly higher in Non-trimetazidine group (52.4%) than Trimetazidine group (21.1%) (Z=4.55;p<0.0001). A study by Kazmi et al showed lesser number of patients in trimetazidine group with TIMI 2 flow post PCI.[21] Studies on direct effect of trimetazidine on TIMI flow in patients undergoing PCI are scarce, however many studies have demonstrated the beneficial effect of trimetazidine in limiting reperfusion injury.

Limitations:

Only ACS patients were included in this study which are known to have higher biomarker levels hence can confound the results. Also, angiographic characteristics ie the type of lesion, multivessel involvement can influence the TIMI flow during PCI. Moreover, the sample size of the study was small.

CONCLUSION:

This study showed that trimetazidine improves the microvascular coronary flow in the patients of AMI undergoing PCI and also leads to significant resolution of ST-T changes on ECG with significant relief from angina post PCI. Larger studies are therefore required in this regard for trimetazidine to be recommended for improvement of coronary microvascular flow and follow -up results in patients of AMI undergoing percutaneous intervention.

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