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Original Article

Role of metabolic manipulator trimetazidine in limiting percutaneous coronary intervention–induced myocardial injury

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ABSTRACT

Background: Trimetazidine (TMZ) is a metabolic modulator that shifts substrate utilization from fatty acid to carbohydrates, thereby, increasing myocardial glucose oxidation and improving myocardial ischemia. We evaluated whether TMZ is effective in reducing myocardial injury after percutaneous coronary intervention (PCI).

Methods: Patients with stable angina undergoing elective PCI were divided into two groups, one who received oral TMZ (35 mg BD) started 7 days before PCI ($n = 48$) and second who did not receive any TMZ (in addition to the standard therapy ($n = 52$)). Troponin-I (cTnI) and creatine kinase–MB (CK-MB) were measured before, 8, and 24 h after PCI. The primary end point was a difference in post-PCI cTnI and CK-MB levels (vs baseline). Frequency of cTnI release in the two groups, total amount of cTnI release, and difference in TIMI flow grade before and after the procedure were also assessed.

Results: Baseline demographics in the groups were comparable. Despite similar baseline levels, post-procedural cTnI was lower at 8 h (0.13 vs 0.56 ng/ml, $p = 0.03$) and 24 h (0.2 vs 1.13 ng/ml, $p = 0.004$) in the TMZ group. Decline or no change in cTnI was significantly more common in the TMZ group (26% vs 2%, $p < 0.01$). Total cTnI released after PCI, as assessed by area under curve was significantly lower in the TMZ group (15.84 vs 3.32 ng h/ml, $p = 0.005$). Although CK-MB levels were also lower in the TMZ group, the difference was not statistically significant. Incidence of post-PCI TIMI 1 or 2 flow was significantly lesser in the TMZ group.

Conclusions: Oral TMZ started 7 days before PCI was effective in limiting PCI-induced myocardial injury with lower cTnI levels and higher prevalence of TIMI-3 flow.

1. Introduction

Percutaneous coronary intervention (PCI) is one of the key treatment strategies for stenotic coronary artery disease. Despite technical advances which have led to decline in the rate of major adverse cardiac events, the incidence of periprocedural/post-procedural myocardial injury (PMI) or necrosis has not substantially decreased.[1,2] About one-third of all elective PCI procedures are followed by rise in cardiac biomarkers representing myocardial injury, which is a marker of adverse events and increased mortality in the follow-up.[3,4] The underlying pathophysiology of PMI involves either side-branch occlusion (proximal PMI, i.e., close to the target lesion) or microvascular obstruction (distal PMI, i.e., in the distal perfusion territory of the target artery).[1] Distal embolism of the atheromatous plaque and thrombotic material, platelet activation with microvasculature plugging, neurohormonal activation, and oxidative stress are all involved in the genesis of PMI. Different cardiac biomarkers have been used to assess the occurrence and the prognostic implications of PMI, and its incidence is influenced by the choice of the cardiac biomarker assay, the criteria used for cut-off values, and the timing and frequency of sampling.

Elevation of creatine kinase–muscle/brain (MB) (CK-MB) above the upper limit of normal has been reported in nearly one-third of patients undergoing elective PCI, whereas cardiac troponins (cTn;

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troponin I and T), which are more sensitive and specific markers of cardiac injury than CK-MB, are abnormal in 30%–70% of cases after PCI.[4–6] Although usually asymptomatic, elevations of cardiac biomarkers after PCI are associated with adverse outcomes and increased mortality during the follow-up.[7–9] The 2007 Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force Universal definition of Myocardial Infarction defined PMI as an elevation of serum biomarkers (preferably cTn) above the 99th percentile upper reference limit (URL), assuming a normal baseline cTn value.[10] The 2012 ESC/ACCF/AHA/WHF Task Force stated that elevations greater than five times 99th percentile URL occurring within 48 h of PCI along with ischemic, angiographic, or imaging findings was Type 4a PCI-related myocardial infarction.[11] When cTn value is $\leq 5 \times$ 99th percentile URL after PCI or when the cTn value is $>5 \times$ 99th percentile URL in the absence of ischemic, angiographic, or imaging findings, the term "myocardial injury" should be used.[11]

Various strategies have been used to reduce the incidence of PMI. These include mechanical approaches such as direct stenting, techniques for stenting bifurcation lesions to prevent side-branch occlusions, and proximal or distal protection devices to prevent embolization of atheromatous debris.[12–16] Pharmacological strategies to protect the myocardium against PMI (cardioprotection) include the use of high-dose statins,[17,18] intracoronary b-blocker[19,20] or adenosine administration,[21,22] cyclosporine A,[23] and remote ischemic preconditioning.[24,25]

Trimetazidine (1-[2,3,4-trimethoxybenzyl-piperazine dihydrochloride]) (TMZ) is a metabolic modulator that was originally developed as an antianginal drug with coronary vasodilatory effects because of its cardioprotective and ischemic preconditioning properties. It modulates mitochondrial homeostasis and also improves myocardial substrate utilization with a shift of energy production from free fatty acids to the more energy efficient pathway of glucose oxidation, by selectively inhibiting mitochondrial long chain 3-ketoacyl coenzyme-A thiolase, a key enzyme in the beta-oxidation pathway.[26] Hence, it can improve myocardial ischemia, and reduce myocardial necrosis with a favorable effect on cardiac biomarkers.

Metabolic manipulation with drugs such as TMZ needs to be initiated well before the PCI so that maximum benefit can be accrued before permanent myocyte damage occurs. Previous studies which have demonstrated the role of TMZ in limiting PMI have used diverse dosing schedules including single oral loading dose started just prior to PCI or maintenance doses initiated few days prior to PCI.[27–31]

2. Aims

This study assessed the effect of oral TMZ (started 7 days before PCI) on PMI by assessing cardiac biomarkers and thrombolysis in myocardial infarction (TIMI) flow in 100 patients with stable angina.

3. Methods

Patients with stable angina scheduled for elective PCI between January and December 2016 at our center were included in the study. The study conformed to the institutional ethical guidelines, and after approval of Institutional Ethics Committee, patients were included after obtaining informed consent.

Assuming that ~45% of patients demonstrate post-PCI rise in troponin and an expected reduction of ~30% with TMZ, the calculated sample size was 102 (alpha error 0.05 and power 80%).

Patients with unstable angina, history of acute coronary syndrome (ACS) in last 6 weeks before enrollment, prior treatment with TMZ, severe liver and renal insufficiency, or left ventricular ejection fraction (LVEF) <40% were excluded from the study.

Patients in both the groups received conventional treatment with antiplatelet drugs, statins, β-receptor blockers, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers, calcium channel blockers, and nitrates. Patients in the TMZ group received oral TMZ (35 mg BD) started at least 7 days before the intervention, whereas controls did not receive TMZ.

All patients underwent baseline investigations, including complete hemogram, renal and liver function test, and blood sugar, serum electrolytes, and lipid profile. Levels of the biomarkers (cTnI and CK-MB) were measured prior to PCI and at 8 h and 24 h after the PCI. Assessment was performed using immunometric luminescent immunoassay with a commercially available reagent (VITROS ECi/ECiQ Immunodiagnostic System; Ortho-Clinical diagnostics, USA; 99th percentile URL: 0.034 ng/mL and 3.38 ng/ml for cTnI and CK-MB, respectively).

All enrolled patients underwent coronary angiography and coronary angioplasty as per institutional protocol using drug-eluting stents. A 12-lead electrocardiogram (ECG) was recorded before, 1 h after PCI, and on the following day. During the procedure, 3-lead ECG was constantly monitored. Occurrence, severity, and duration of chest pain, in addition to episodes of acute ST elevation or depression, were recorded.

3.1. End points

The primary end point was a difference in post-PCI cTnI and CK-MB levels (as compared with the baseline) between the TMZ and control groups. The secondary end points were the frequency of cTnI release in the two groups, the total amount of cTnI release, and any difference in TIMI flow grade before and after the procedure in the two arms.

3.2. Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD), and categorical variables, as percentage. Student's t test and Chi-square analysis were carried out for comparison of continuous and categorical variables, respectively, and p value < 0.05 was considered significant. All statistical analyses were performed using IBM SPSS Statistical Software (IBM SPSS Statistics, version 20.0; IBM SPSS, USA).

4. Results

A total of 120 patients were included; after the initial coronary angiogram, eight patients from the TMZ arm and six from the control group were referred for coronary artery bypass surgery, and three patients from each group did not require PCI because of insignificant coronary stenosis. The final population analyzed included 48 patients in the TMZ group and 52 in the control group. Pretreatment with TMZ was well tolerated in all patients, and there was no drug-related adverse effects necessitating drug discontinuation or reduction in dose.

4.1. Demographic characteristics and baseline medications

The mean age of the patient population was 56.9 ± 9.8 years, and 79% were male. Overall, 36% had diabetes and 46% had hypertension, whereas a previous history of MI was present in 48% of patients. There was no significant difference in the TMZ and control groups in terms of age, gender distribution, body mass index, prevalence of diabetes, hypertension, lipid levels, and baseline LVEF. Both the groups were also comparable with regard to use of

cardiac medications including antiplatelet drugs, statins, β-receptor blockers, ACEI, and nitrates. Detailed demographics are given in Table 1.

4.2. Angiographic characteristics

The angiographic complexity of lesions, target vessel distribution, and mean syntax score were not significantly different in the two groups. The distribution of single- (50 vs 46.1%), double- (43.7 vs 40.3%), and triple-vessel disease (6.2 vs 13.4); % of diameter stenosis (89 vs 92%); mean number of stents used per patients (1.8 vs 1.6); mean total stent length (42.2 mm vs 39.2 mm); and mean inflation pressure used (9.3 vs 9.1 atm) were also comparable with no significant difference among the two groups. The PCI procedure was successful in all patients with no cases of major side-branch occlusion, dissection, or stent thrombosis (Table 2).

4.3. Temporal change in postprocedural cTnI levels

Despite similar baseline cTnI levels in both groups, levels at 8 h (0.13 ± 0.23 vs 0.56 ± 1.37 ng/ml, $p = 0.03$) and 24 h (0.2 ± 0.31 vs 1.13 ± 2.23 ng/ml, $p = 0.004$) were significantly lower in the TMZ group than the controls (Fig. 1).

Overall, 37/52 (71.1%) patients in the control group had troponin rise > URL after PCI in comparison with 19/48 (39.5%) in the TMZ group ($p = 0.04$). The proportion of patients with a decline or no change in cTnI from baseline values was also significantly higher in the TMZ group in comparison with controls (26% vs 2%, $p < 0.01$). Of the 100 patients, 43 had post-PCI elevation of cTnI >5 times ULN. Of these, 30/52 (57.6%) were in the control group, whereas 13/48 (27%) were in the TMZ group, $p = 0.03$.

We calculated the area under curve (AUC) of postprocedural total cTnI release in each group. The AUC of cTnI was significantly higher in the control group than in the TMZ group (15.84 VS 3.32 ng h/ml, $p = 0.005$).

4.4. Temporal change in postprocedural CK-MB levels

Although post-procedural CK-MB levels were lower in the TMZ group at 8 h (2.51 ± 1.99 vs 2.71 ± 5.75, ng/ml) and 24 h (3.00 ± 2.71 vs 4.43 ± 6.95 ng/ml), the trends were not statistically significant ($p = 0.81$). (Fig. 2).

4.5. Changes in TIMI flow after PCI

Before PCI, TIMI 1 or 2 flow was present in 23/48 (47.9%) patients in the TMZ group as compared with 24/52 (46.1%) in the controls, $p = 0.86$. However, after PCI, significantly less number of patients in the TMZ group had TIMI 2 flow (6/48, 12.5%) than those in the control group (14/52, 26.9%), $p = 0.04$. After PCI, 63% of TMZ patient converted from pre-PCI TIMI 1/TIMI 2 flow to post-PCI TIMI 3 flow, whereas this was observed in only 38% of controls.

4.6. Predisposing factors for PMI

Various patient- and lesion-related factors including patient age, diabetes, hypertension, renal impairment, angiographic complexity of lesions, and syntax score were analyzed in patients with and without cTnI release after PCI (Table 3). Patients with cTnI release after PCI had more frequent presence of complex lesions and TIMI 2 flow, whereas there were no significant differences in any other variables in the two groups.

4.7. In-hospital events

No cases of postprocedural ST elevation MI, stent thrombosis, or redo-PCI were encountered, and there were no deaths in either of the two groups.

5. Discussion

Our study demonstrates that in patients with stable angina undergoing elective PCI, oral TMZ administered for 7 days before PCI significantly reduces postprocedural cTnI release at 8 h and at 24 h. Although most patients (98%) in the control group had a rise in cTnI within 8–24 h (in comparison with baseline values), 26% patients in the TMZ group exhibited no change or even a decline in cTnI following PCI ($p = 0.01$). After PCI, significantly more patients in the control group (71.1%) had a rise in cTnI (>99th percentile of ULN) than those in the TMZ group (39.5%). An elevation of cTnI value greater than five times 99th percentile ULN occurred more

Table 1
Demographic characteristics and baseline medications.

Variable	TMZ group ($n = 48$)	Control group ($n = 52$)	p value
Age (yrs)	57.6 ± 9.5	56.3 ± 10.1	0.51
Male	36 (75)	43 (82.6)	0.35
BMI (Kg/m2)	19.8 ± 3.6	20.1 ± 3.2	0.66
EF (%)	54.7 ± 10.6	56.6 ± 10.5	0.37
Creatinine (mg/dl)	1.0 ± 0.4	1.0 ± 0.3	1.00
Diabetes	17 (35.4)	19 (36.5)	0.91
Current smoking	10 (20.8)	9 (17.3)	0.65
Hypertension	21 (43.7)	25 (48)	0.66
Previous MI	29 (60)	19 (36.5)	0.017
Total cholesterol (mg/dl)	204.5 ± 56.8	214.7 ± 43.6	0.32
Triglyceride (mg/dl)	112.8 ± 49.2	108.8 ± 46.6	0.68
HDL (mg/dl)	35.6 ± 11	38.5 ± 13	0.23
LDL (mg/dl)	112.2 ± 39.4	115.8 ± 44.7	0.67
VLDL (mg/dl)	57.7 ± 18.9	61.4 ± 25.2	0.41
Aspirin	48 (100)	51 (98)	0.33
Clopidogrel	21 (43)	20 (38.4)	0.59
Beta blocker	42 (87.5)	45 (86.5)	0.89
Statins	46 (95.8)	46 (88.4)	0.17
ACE-I	29 (60.4)	27 (51.9)	0.39
Nitrates	37 (77)	37 (71.1)	0.50

All values are expressed in mean ± standard deviation. Values in parenthesis indicate %. ACE-I, angiotensin-converting enzyme inhibitor; BMI, body mass index; EF, ejection fraction; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; VLDL, very low–density lipoprotein.

Table 2
Baseline angiographic characteristics.

Variable	TMZ group ($n = 48$)	Control ($n = 52$)	p Value
Lesion class A + B1	26 (54.1)	29 (55.7)	0.87
Lesion class B2 + C	22 (45.8)	23 (44.2)	0.87
Left main	0 (0)	0 (0)	–
LAD	32 (66.6)	29 (55.7)	0.26
LCx/OM	21 (43.7)	24 (46.1)	0.81
RCA	26 (54.1)	29 (55.7)	0.87
Diagonal	6 (12.5)	4 (7.6)	0.42
Bifurcation lesion	3 (6.25)	2 (3.8)	0.58
Syntax score	17.4 ± 5.6	17.8 ± 4.9	0.71
Number of stents per patient	1.8 ± 0.9	1.6 ± 0.7	0.22
Stent Length (mm)	42.2 ± 25.0	39.2 ± 21.6	0.52
Stent Diameter (mm)	2.9 ± 0.2	3.0 ± 0.3	0.48
SVD	24 (50)	24 (46.1)	0.70
DVD/TVD	24 (50)	28 (53.8)	0.70
Mean inflation pressure (atm)	9.3 ± 1.8	9.1 ± 1.9	0.59
Pre PCI TIMI 0 flow	0 (0)	0 (0)	–
Pre PCI TIMI 1 flow	5 (10.4)	4 (7.6)	0.62
Pre PCI TIMI 2 flow	18 (37.5)	20 (38.4)	0.92
Pre PCI TIMI 3 flow	25 (52.0)	28 (53.8)	0.85

All values are expressed in mean ± standard deviation. Values in parentheses indicate %. DVD, double-vessel disease; LAD, left anterior descending artery; LCx, left circumflex artery; OM, obtuse marginal artery; RCA, right coronary artery; SVD, single-vessel disease; TVD, triple-vessel disease; PCI, percutaneous coronary intervention.

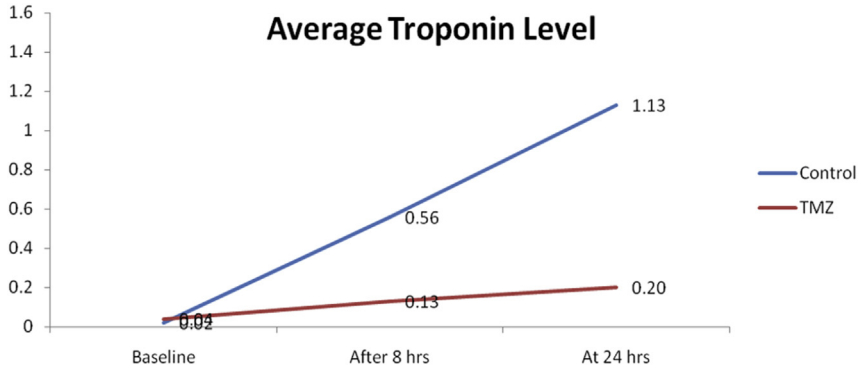

Fig. 1. Troponin levels at the baseline, 8, and 24 hrs after PCI in the control and TMZ group (P 0.03 for comparison between the two groups at 8 hrs and 0.004 at 24 hrs). TMZ, trimetazidine; PCI, percutaneous coronary intervention.

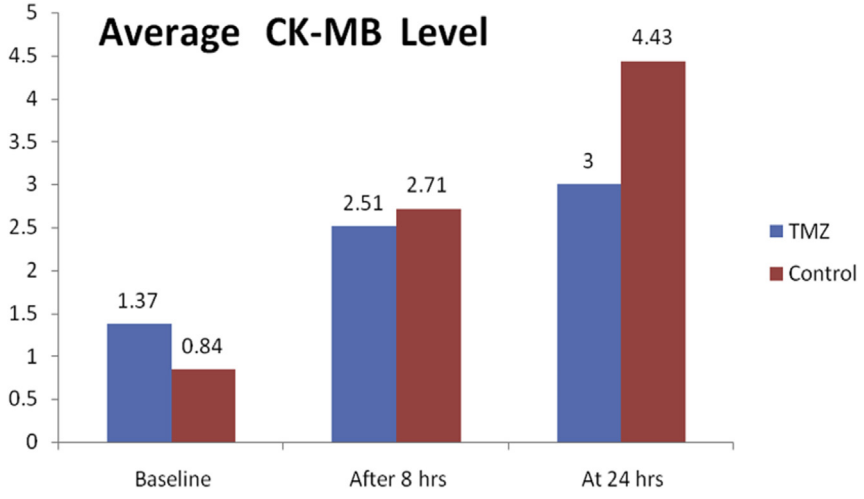

Fig. 2. CK-MB levels at the baseline, 8, and 24 hrs after PCI in the control and TMZ group (P, not significant). CK-MB, creatine kinase–MB; TMZ, trimetazidine; PCI, percutaneous coronary intervention.

Table 3
Characteristics of patients with and without post-PCI cTnI elevation.

Characteristics	$n = 44$, cTnI at 24 h < ULN	$n = 56$, cTnI at 24 h > ULN	p value
Age (yrs)	56.9 ± 10.0	57.0 ± 9.7	0.96
Diabetes	19 (43.1)	17 (30.3)	0.18
Hypertension	22 (50)	24 (42.8)	0.47
Creatinine (mg/dl)	1.1 ± 0.4	1.0 ± 0.3	0.55
A + B1 lesion	30 (68.1)	25 (44.6)	0.01
B2 + C lesion	14 (31.9)	31 (55.0)	0.01
Stent length (mm)	36.3 ± 20.4	44.2 ± 25.0	0.09
Multivessel intervention	16 (36.3)	26 (46.4)	0.31
Final TIMI-2 flow	0 (0)	20 (35.7)	<0.001
Final TIMI-3 flow	44 (100)	36 (64.2)	<0.001
Received TMZ	29 (65.9)	19 (33.9)	0.001

All values are expressed in mean ± standard deviation. Values in parentheses indicate %. PCI, percutaneous coronary intervention; cTnI, troponin-I; TMZ, trimetazidine; ULN, upper limit of normal.

frequently in controls (57.6%) as compared with the TMZ group (27%, $p = 0.03$). 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.[11]

Although usually asymptomatic, even minor degrees of post-PCI myocardial necrosis have significant prognostic implications, and the magnitude of rise in cardiac biomarkers (especially Tn-I) has been reported to directly correlate with adverse events in the follow-up.[3,4]

Previous reported studies of TMZ in patients undergoing PCI have used different dosing schedules for various durations of time. Polonski et al[27] initially reported the use of oral TMZ, 60 mg daily, administered at least 4 days before PCI in patients of stable angina with single vessel disease. Although angina, rhythm disturbances, and ischemic ST-T changes were reduced by TMZ, there was only a nonsignificant trend to lower levels of cTnI at 6 and 12 h after the PCI. The beneficial effects of a single loading dose of 60 mg of TMZ before PCI in patients with stable angina on postprocedural frequency and level of cTnI release was first reported by Bonello et al.[28] Despite no statistically significant difference between the frequency of cTnI increase between the two groups, post-PCI cTnI levels were significantly lower in the TMZ group at all the time points assessed. The total amount of cTnI released after PCI, as assessed by the AUC of serial measurement, was also significantly lower in the TMZ group. This is similar to what was observed by us (AUC of cTnI 15.84 vs 3.32 ng h/ml, $p = 0.005$, in controls vs TMZ group).

The cardioprotective role of TMZ in limiting PMI has also been assessed in patients with ACS. Labrou et al[29] assessed the effect of TMZ on biomarker release pattern and echocardiographic LV function after PCI. Patients received 20 mg oral TMZ every 8 h, starting 15 days before PCI and continued for 3 months thereafter. The frequency of cTnI >1 ng/ml and CK-MB >5 ng/ml at 24 h after PCI was 26% vs 44% and 22% vs 40% in the TMZ and control groups, respectively. The number of patients with LVEF <50% was also significantly lower in those receiving TMZ at 1 and 3 months. Xu et al[30] randomized patients with unstable angina to the oral TMZ (60 mg loading 0.5–1.0 h before PCI followed by 20 mg three times daily) or the control group. Not only did patients on TMZ have lower cTnI levels at 16–18 h, but the proportion of patients with post-PCI cTnI levels > 0.10 mg/L was also significantly lower than in the controls. In a combined patient population of stable and unstable angina pectoris, Chen et al randomized patients to preprocedural oral TMZ (20 mg three times a day) for 5 ± 2 days before PCI followed by a loading dose of 60 mg 30 min before PCI, and continued for 4 weeks thereafter.[31] Although biomarkers were not measured, administration of TMZ was associated with significantly less frequent angina (0% vs 25.5%), ST-T changes (60.8% vs 78.3%) and higher postprocedural LVEF at 4 weeks (66.6 ± 7.1% vs 63.0 ± 7.7%).

Combination TMZ therapy with high-dose atorvastatin has also been reported to lower post-PCI biomarkers including cTnI, myeloperoxidase high-sensitivity C-reactive protein, tumor necrosis factor-α, and serum interferon-γ levels.[32,33]

In a meta-analysis of nine randomized trials of 778 patients undergoing PCI, Zhang et al[34] reported that periprocedural administration of TMZ not only significantly improved LVEF but also reduced elevation in cTnI level (relative risk [RR], 0.69), angina episodes during PCI (odds ratio [OR], 0.16), and ischemic ST-T changes on the ECG during PCI (RR, 0.76; 95% confidence interval, 0.59–0.98).

5.1. Predisposing factors of PMI

Various patient-, lesion-, and procedure-related factors have been identified to determine the incidence and magnitude of PMI. These include older patient age, multivessel diffuse coronary artery disease, preexisting renal impairment, anemia, higher plaque burden and number of lesions, complexity of lesions (eg., bifurcation lesions, tortuous lesions), suboptimal stenting, and multiple stents. However, we observed no significant differences in any patient- or lesion-related variables among patients with or without post-PCI cTnI release. The role of TMZ in such a high risk patient population was assessed by Shehata et al[32] among diabetic patients with preexisting chronic kidney disease undergoing elective PCI, oral TMZ 35 mg BD for 72 h, started 48 h before PCI, significantly reduced pos-procedural cTnI levels at 6,12, and 24 h.

5.2. Effect on TIMI flow

Although various studies have assessed the role of TMZ on PMI by measuring cardiac biomarkers, data on TIMI flow after PCI are scarce. We observed that TMZ resulted in lesser incidence of postprocedural TIMI 2 flow (12.5% vs 26.9%). Nearly two-third of patients on TMZ converted from pre-PCI TIMI 1/2 flow to post-PCI TIMI 3 flow as compared with only one-third of controls.

Various mechanisms may explain the prevention of ischemic reperfusion injury by TMZ including its ability to inhibit opening of mitochondrial permeability transition pores, a key event in cardiomyocyte death after ischemic myocardial reperfusion.[35] Experimental studies have demonstrated that TMZ inhibits coronary microembolization and myocardial apoptosis leading to a cardioprotective effect.[36,37] Favorable modulation of cardiac energy metabolism by shifting it from fatty acid oxidation to glucose

oxidation helps preserve ATP levels and prevents ischemic injury induced myocardial necrosis.[26,38,39]

6. Limitations

Only patients with stable angina were included as patients with ACS are likely to have high preprocedural biomarker levels, confounding the results. Further studies with larger number of patients with stable and unstable angina and incorporation of end points such as TIMI frame count analysis are warranted to clarify the role of TMZ in patients undergoing PCI. More data are need to identify the optimal duration (pre- and post-PCI) and dose of TMZ that needs to be administered.

7. Conclusions

Oral TMZ started before elective PCI in patients with stable angina reduces peri-PCI myocardial injury with significant reduction in cTnI levels measured serially. Significantly more patients (26% vs 2%) on TMZ exhibited no change or decline in cTnI following PCI than controls. The total amount of cTnI released after PCI (as assessed by AUC) was also significantly lower in the TMZ group. These effects on cTnI levels translated into better post-PCI TIMI flow and higher conversion from pre-procedure TIMI 1/2 flow to post-PCI TIMI 3 flow.

Conflict of interest

None of the authors have any financial or other disclosures to declare.

Ethics

The study conformed to the institutional ethical guidelines, and after approval of Institutional Ethics Committee, patients were included after obtaining informed consent.

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