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Role of Trimetazidine in Prevention of Coronary No Reflow in Patients with ST Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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Abstract:

BACKGROUND:

The efficacy of trimetazidine (TMZ) in chronic coronary syndrome has been well demonstrated butdata regarding TMZ in managing acute myocardial infarction (AMI) remain unclear. So, in our study we aimed to evaluate the role of TMZ in prevention of coronary no-reflow in STEMI patients undergoing primary Percutaneous Coronary Intervention.

METHODS:

A Prospective observational open label case control study was conducted on 200 STEMI patients who underwent PPCI. They were subdivided to 2 groups: Group I (control group): 100 patients who were not treated with TMZ. Group II (TMZ group): 100 patients who were treated by trimetazidine before and after PPCI for 1 month. All patients were assessed clinically, angiographically, ECG, Full labs and baseline echocardiography and after 1 month.

RESULTS:

There was a trend towards lower Incidence of coronary no reflow in the TMZ group (13%) as compared to the control group (18%) however it did not reach statistical significance (P-value= 0.32). TMZ group showed highly significant resolution of ST segment elevation in ECG after 24 hours as compared to the control group (P value=0.002). The TMZ group also showed **statistically** significantly improvement of LV ejection fraction as compared to the control group at 1 month follow up echocardiography (P-value=0.012).

CONCLUSIONS:

Although TMZ showed no significant improvement in TIMI flow in STEMI patients who underwent PPCI, however it was associated with greater resolution of ST segment elevation on ECG and improvement of LV systolic function (EF% and GLS by speckle tracking) after 1 month.

Key words: STEMI, Coronary no-reflow, Trimetazidine, GLS.

Background:

Ischemic heart diseases are at the top of the list of top 10 causes of death worldwide[1]. Acute Coronary Syndromes (ACS) (including ST-segment elevation myocardial infarction (STEMI), NSTEMI and unstable angina) are considered as universal huge medical, social, and economic burden[2,3]. Primary percutaneous coronary intervention (PPCI) is the gold standard treatment of STEMI[4]. Advancement of PPCI techniques, devices and pharmacological drugs have resulted in restoring thrombolysis in myocardial infarction with TIMI 3 flow in most of patients, however there remains a small percentage of STEMI patients who have overt impairment of myocardial reperfusion despite successful opening of infarct related epicardial artery (IRA). This phenomenon is known as no-reflow (NR)[5]. NR is defined as suboptimal myocardial reperfusion through a part of the coronary circulation without angiographic evidence of mechanical vessel obstruction[6]. Consequences of NR include chest pain, malignant arrhythmias, hypotension, heart failure, acute pulmonary oedema and increased long term 5 years mortality[6,7]. Therefore, Coronary no reflow remains a nightmare for doctors who perform PPCI for STEMI patients, hence ongoing attempts to understand, prevent and treat coronary no reflow in patients with STEMI undergoing primary PCI[8]. Two thirds of the energy of the heart are produced form free fatty acid oxidation and the rest is derived from glucose oxidation and lactate[9]. During ischemia, free fatty acid oxidation increases and glucose oxidation is decreased. Despite producing almost the same quantity of ATP, fatty acid oxidation requires an

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additional 10–15% of oxygen, which represents a significant pitfall under ischemic conditions[10]. These process leads to a decrease of ATP available for myocardial contraction, as well as increased cell acidosis and calcium overload which lead to increased incidence of myocardial injury[10,11]. Trimetazidine (TMZ) has a selective inhibitory effect on long chain 3-ketoacyl CoA thiolase activity, which is responsible for the last stage of fatty acyl beta-oxidation leading to reduce fatty acid oxidation and stimulating glucose oxidation without producing any negative inotropic effect. TMZ has been shown to increase the phosphocreatine (PCr)/ATP ratio by 33 %, indicating preservation of myocardial high-energy phosphate levels[11,12]. Multiple animal studies have demonstrated the ability of TMZ to limit ischemia–reperfusion injury and decrease the incidence of coronary no reflow[13–15]. In human the efficacy of TMZ in chronic coronary syndrome has been well demonstrated[16] but data regarding the clinical effect of TMZ in managing acute myocardial infarction (AMI), prevention of reperfusion injury and prevention of coronaries no reflow are limited and remain unclear. Therefore multiple trials attempt to justify role of TMZ in acute coronary syndrome[17].

Materials and Methods:

Our prospective observational open label case control study started January 2019 till April 2021. The study was conducted on 200 patients who presented to Ain Shams university hospitals with STEMI and underwent PPCI to the culprit vessel with no other significant lesions in the other coronaries. We aimed in this study to evaluate the role of trimetazidine in prevention of coronary no-reflow in STEMI patients who underwent PPCI.

The patients were subdivided to two groups: **Group I (control group):** 100 patients who were not treated with TMZ**.Group II (TMZ group):** 100 patients who were treated by 60 mg loading trimetazidine before PPCI followed by TMZ 35 mg BID for 1 month. All patients were pre- treated with aspirin (300mg) and Clopidogrel (600mg) before the procedure[18,19] and maintained on optimized medical therapy according to ESC 2017 STEMI guidelines[4]. Physicians performed the procedure were blinded to the random assignment.

The study included STEMI patients below 70 years of both genders who underwent PPCI. Exclusion criteria included patients with completed STEMI > 48 hours without residual chest pain, patients who received thrombolytic therapy before PPCI, patients with severe renal impairment (creatinine clearance <30ml/min), patients with Parkinson's disease, trimetazidine hypersensitivity, incomplete revascularization, above 70 years old and patients who underwent more than one balloon inflation or whom thrombus aspiration device was used during PCI or patient refusal to join the study.

All the patients were subjected to the following: 1. **Complete history taking** focusing on CVD risk factors and pain to door time. 2. **Clinical examination and follow up for 1 month**. 3.**12 lead surface ECG:** on admission and after 24 hours to assess resolution of ST segment. 4. **Laboratory investigations:** Routine labs included (Complete Blood picture, Kidney function tests, Lipid profile, Hemoglobin A1 C and daily cardiac enzymes including troponin). 5. **Transthoracic Echocardiography (TTE):** 1 day after PPCI and follow up after 1 month, with the special comment on: Ejection fraction: Manual and semi-automated tracing was used to measureLV ejection-fraction (by modified Simpson method), LV diastolic Functions by Tissue doppler (E/E'),[20] and 2D LV strain (Digital loops were acquired from apical 2-, 3- and 4-chamber and Para sternal short axis views. Peak Global longitudinal strain (GLS) was calculated from offline analysis using a computer software for tissue tracking[21]). 6. **Full Angiographic and interventional details of PPCI** (Culprit intervention Vessel, Non-Culprit lesions, thrombus burden, PCI technique, TIMI Flow pre and post PCI[22], stent length and diameter and post PCI complications).After the PPCI patients in both groups divided into patients with normal coronary artery flow (TIMI III flow) and patients with coronary no-reflow (TIMI 0, I and II flow).Physicians who classified patients according to TIMI flow were blinded of the random assignment and different than those performed the procedure.

Our primary end point was Incidence of no reflow in both groups. While our secondary end of point was assessment of ST segment resolution in ECG, Peak, descent of cardiac enzymes and troponin, LV systolic, diastolic function at day 1 and after 1 month, infarct size by longitudinal speckle tracking (GLS) at day 1 and after 1 month. Follow up for MACE was done for 1 month.

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Statistical analysis: Data Were collected, tabulated and subjected to statistical analysis using SPSS.

Results:

No statistically significant difference was found between both studied groups regarding age, gender and BMI. The mean age of **Control group** was 54.79 ± 7.92 years, 74% were males and 26% were females, while the mean age of the **TMZ group** was 54.98 ± 8.08 years, 68% were males and 32% were females **(Table 1)**.

No statistically significant difference was found between the 2 studied groups regarding cardiovascular risk factors as shown in **(Table 2)**.

No statistically significant difference was found between the 2 studied groups regarding pain to door, STEMI territory, culprit vessel, site of occlusion, thrombus burden, TIMI flow pre PPCI and Killip classification. Incidence of coronary no reflow post PCI was lower in TMZ group (13%) as compared to control group (18%) but without reaching statistical significance (P-value= 0.32) as shown in **(Table 3)**.

Regarding the baseline laboratory profile, no statistically significant difference was found between the control group and TMZ group **(Table 4)**.

No statistically significant difference was found between the 2 studied groups regarding ST segment on baseline ECG and baseline cardiac enzymes. There was also no statistically significant difference between the 2 studied groups regarding cardiac enzymes after 24 hours. However, the TMZ group showed a statistically significant greater resolution of the ST segment after 24 hours as compared to the control group (P-value=0.002) **(Table 5)**.

Regarding PCI technique: crossing balloon without inflation before stenting was done in 90 patients in TMZ group as compared to 95 patients in control group with no statistically significant difference (P-value=0.17). While PTCA once before stenting was done in 48 patients in TMZ group as compared to 59 patients in control group with no statistically significant difference (P-value=0.19). There was also no statistically significant difference between the 2 studied groups regarding the stent diameter and length (P-value=0.17 and P-value= 0.06 respectively) **(Table 6)**.

No statistically significant difference was found between the control group and TMZ group regarding left ventricle systolic function (EF%) as calculated by Simpson's method (P-value =0.31) and LV GLS by speckle tracking echocardiography (P-value=0.11) at day 1 after PPCI. Assessment of LV diastolic function by tissue doppler ($E/e^{'}$) showed higher $E/e^{'}$ in control group (10.93 ± 1.41) as compared to TMZ group (mean is 9.97 ± 1.92), with statistically significant difference (P-value=0.03)**(table 7**).

Follow up echocardiography after 1 month showed a trend towards higher LVEF% in TMZ group as compared to control group, however it did not reach statistical significance (P-value=0.09). GLS by Speckle tracking echocardiography after 1 month was higher in TMZ group as compared to the control group with highly significant difference (P-value=0.008).

Assessment of LV diastolic function by tissue doppler ($E/E^{'}$) on follow up echocardiography after 1 month showed higher $E/E^{'}$ in control group (10.87 ± 1.38) as compared to TMZ group (mean is 9.73 ± 1.80), with highly statistically significant difference (P-value=0.008) **(Table 8)**.

There was no statistically significant difference found between the control group and TMZ group regarding the percentage of changes of LV diastolic function by TDI ($E/E^{'}$), GLS by speckle tracking echocardiography and cardiac enzymes.

There was a statistically significant percentage of change in improvement of LVEF % on follow up echocardiography after 1 month post PPCI in the TMZ group as compared to control group (P-value=0.012). There was also statistically significant greater percentage of descent of CK -total in TMZ group as compared to the control group (P-value=0.000). Percentage of resolution of ST segment on ECG after 24 hours in TMZ group was also highly statistically significant as compared to the control group (P-value=0.000) **(Table 9)**.

Clinical follow up of patients for 1 month in OPD showed that there was no mortality nor Post MI angina (CCSIII/IV) in both groups, more patients complained of exertional dyspnea NYHA III/IV in the control group as compared to the TMZ group but with no statistically significant difference (P-value=0.79). The incidence of arrhythmias in the form of AF was higher in control group as compared to TMZ group but also with no statistically significant difference (P-value=0.65) **(Table 10)**.

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Discussion:

In the present study, there was a trend towards lower incidence of coronary no reflow in TMZ group (13%) as compared to control group (18%), however it did not reach significant value. This is in agreement with the finding of ***Khaled et al.*** who conducted a study on 40 patients undergoing primary PCI for acute STEMI.Twenty patients of them received trimetazidine before primary PCI (study group) and the other twenty patients did not receive trimetazidine (control group), to assess effect of trimetazidine on myocardial salvage index in STEMI patients undergoing primary PCI. The study concluded that post procedural TIMI 3 flow was more among the study group (12 vs. 9) yet the difference was not statistically significant[23]. ***Bonello, L. et al.*** conducted a study on 266 ACS patients, where 136 patients were assigned to the TMZ group and 130 to the control group. The study showed that incidence of coronary no reflow was less in TMZ group than in the control group with no statistically significant difference (P-value =0.26)[24]. ***Kutala et al*** who conducted study on isolated rat hearts, showed that the untreated control hearts subjected to 30 min of global ischemia followed by 45 min of reperfusion showed a significant decrease in Coronary Flow (41%) as compared to hearts treated with IV TMZ which did not show any significant differences in the recovery of Coronary flow[25].This may be explained by the fact that efficacy of TMZ may depend on the patient status, dosage, route of administration, time of administration and different studied living being e.g.(humans, rats and rabbits).

In our study, TMZ group showed a highly statistically significant resolution of ST segment elevation on ECG after 24 hours as compared to the control group (P-value=0.002). This is in agreement with **Steg, P. G. *et al***. who conducted a study on 94 patients with STEMI who were randomized to receive trimetazidine (40 mg bolus followed by 60 mg/day intravenously for 48 h) (n=44) VS placebo (n=50), starting before recanalization of the infarct vessel by primary angioplasty. The study showed earlier resolution of ST segment elevation in the treated group where the authors suggested that TMZ may be associated with earlier, improved myocardial reperfusion and reduced reperfusion injury of infarcted myocardium[26].**Dong *et al.*** in his study on AMI patients, who were randomized to receive 60 mg TMZ followed by 20 mg 3 times daily for 2 weeks (n = 32) or to be controls (n = 28), showed marked return of ST segment towards baseline one hour after reperfusion therapy in the trimetazidine group than in the control group (P-value = 0.04)[27].

In our study baseline troponin and after 24 hours after PCI was lower in TMZ group as compared to the control group but did not reach statistical significance. This is in line with **Chun, K. J. *et al.*** who conducted study on 13,733 AMI patients and showed that peak troponin I was lower (44.2 ± 65.2) in TMZ group comparing to TMZ non-users group (48.1 ± 85.9) with no significant difference (P-value= 0.197)[17]. **Bonello, L. *et al***. conducted a study on 266 ACS patients, where 136 patients were assigned to the TMZ group and 130 to the control group. The study showed that the AUC of post-procedural cTnI was significantly higher in the control group than in the TMZ group (P-value <0.05)[24]. **Qian, G. *et al*** who conducted study on 173 STEMI patients who randomly received trimetazidine (n=87) or placebo (n= 86) to assess infarction size by CMR, showed troponin after 24 hours was significnatly lower in TMZ group (P-value = 0.34), despite baseline troponin is higer in TMZ group than placebo group with no significnat value (P-value=0.76)[28]. This differnce may be atrributed to different pain to door time in study population, different types tropinin (C,T, and I)and different types of ACS of studied populations which included STEMI, NSTEMI and unstable angina.

In the present study, descent of CK-total within 24 hours in TMZ group was highly statistically significant as compared to the control group (P=0.00). This is concordant with **Li, R. *et al.*** who reported significant reduction of CK-total on the second day in TMZ group compared to control group[29]. Also **Rebrova, T. Y. *et al.*** on his study on 79 patients with AMI who received thrombolytic therapy. The study concluded that total CK after 24 hours was significantly lower in TMZ group than the control group (P-value=0.001)[30].

In the present study no statistically significant difference was found between control group and TMZ group regarding baseline echocardiographic parameters including: left ventricle systolic function (EF%) calculated by 2D Simpson's method and GLS by speckle tracking echocardiography. This is in concordant with the finding**Steg, P. G. *et al*** who showed no significant difference at 0 and 14 days Ejection Fraction between TMZ group and placebo group, (P-value=0.67)[26]. **Bonello, L. *et al.*** also showed no significant difference in baseline LVEF% regarding both groups (P-value =0.7)[24]. This might be attributed to stunning of the myocardium early after the MI even after successful PPCI.

Assessment of LV diastolic function by tissue doppler (E/E') in follow up echocardiography after 1 month showed higher E/e' in control group (10.87 ± 1.38) as compared to TMZ group (9.73 ± 1.80) with highly statistically significant difference (P-value=0.008). This is concordant with the study of **Fedulaev, Y. N. *et al.*** who concluded that Trimetazidine 70 mg daily in the 2 month treatment of diastolic heart failure in patients with IHD and hypertension resulted in significant improvement of some indicators of mitral blood flow only in patients with type I

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diastolic dysfunction[31]. **Vitale, C.** ***et al.*** in his study concluded that trimetazidine added to standard medical therapy had a beneficial effect on LV systolic and diastolic functions in elderly patients with ischemic cardiomyopathy[32].

On the contrary, **Demirelli, S.** ***et al*** showed no significant effect of TMZ on NSTEMI patients (60 mg TMZ just prior to PCI and continued for one month after the procedure) regarding Tissue Doppler parameters used for the assessment of diastolic functions[33].This might be attributed to conduction of the study on NSTEMI patients who tend to have more diffuse CAD and multivessel affection as compared to STEMI patients [34].

Our study showed statistically significant percentage of change regarding improvement of LV ejection fraction in TMZ group as compared to control group after 1 month follow up echocardiography (P-value=0.012). Also, GLS by Speckle tracking echocardiography after 1 month was statistically significantly higher in TMZ group as compared to control group, (P-value =0.008). GLS has been shown to be more accurate than conventional EF in detection of impairment of LV function, less operator dependent and it also gives additional information about prognosis [35].**Shehata** who studied 100 Diabetic anterior STEMI patients who were randomly assigned to receive oral trimetazidine (70 mg then 35mg bid) (group A, 50 patients) or placebo (group B, 50 patients), starting before thrombolysis[36]. reported significant improvement of LVEF % after 6 months among TMZ group. **Qian, G.** ***et al.*** reported that TMZ treatment initiated prior to primary PCI could reduce infarction size and microvascular obstruction (MVO), and make improvement of myocardial salvage index(MSI) in STEMI patients assessd by CMR[28].

1 month clinical follow up of the patients in both groups in the present study showed that incidence of exertional dyspnea (NYHA III-IV) and AF was higher in the control group as compared to the TMZ group but with no statistically significant difference. The retrospective analysis of **Chun, K. J. et al** who reported that TMZ in patients with AMI decreased the total MACE by 76% and all-cause mortality risk by 59% over a year follow-up[37]. Also the meta-analysis of **Li, Y. et al** concluded that adjunctive trimetazidine therapy played a significant role on reduction of the total MACE in patients with AMI[38].

Infarct size is an important factor of mortality in STEMI patients , so decrease the infarct size in STEMI is a major therapeutic target[39]. Multiple trials documented the positive impact of TMZ on LVEF, and reduction of reperfusion damage in STEMI patients[29,36,40]. TMZ treatment prior to PCI results in improvements in left ventricular end-diastolic volume and decrease in brain natriuretic peptide (BNP) level in patients with AMI[33]. Also, previous animal experiments showed that TMZ reduce infarction size in animalmodels[13–15]. All of these trials were in agreement with the results of our study.

The positive impact of TMZ on the LV function as well as on ST segment resolution and rapid decline of cardiac enzymes could be attributed to the effects of TMZ. TMZ may reduce reperfusion myocardial injury especially in the acute ischemia-reperfusion phase through various mechanisms including: FFA breakdown inhibition and glucose breakdown stimulation, reduction in the amount of oxygen necessary for ATP production, reduction in the cellular accumulation of Na+ and Ca 2+, reduction in ATP losses for maintaining ion homeostasis, reduction of adverse effects of overloading cells with calcium, cardiomyocyte apoptosis inhibition, reduction of granulocyte infiltration to the reperfused and ischemic area of the myocardium, reduction in the cellular accumulation of lactic acid and H+ and anti-radical effect [41].

Conclusion:

Although TMZ showed no significant improvement in TIMI flow in STEMI patients who underwent PPCI, however it was associated with greater resolution of ST segment elevation on ECG, rapid descent of CK-total within 24 hours and improvement of LV systolic function (EF% and GLS by speckle tracking) after 1 month.

Limitation:

This study was a single center study with relatively small size sample. Patients were treated with clopidogrel not Ticagrelor or prasugrel. No long term follow up of echocardiography after 3 or 6 months. Not all follow up echocardiography were performed exactly at 30 days after PPCI.

Conflicts of interest:

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Tables:

Table (1): Demographic characteristics of the Studied Groups.

		Control group	TMZ group	Test value	P-value	Sig.
		No. = 100	No. = 100			
Age (years)	Mean ± SD	54.79 ± 7.92	54.98 ± 8.08	0.168•	0.867	NS
	Range	25 – 69	32 – 69			
Gender	Female	26 (26.0%)	32 (32.0%)	0.874*	0.350	NS
	Male	74 (74.0%)	68 (68.0%)			
BMI (Kg/m^2)	Mean ± SD	24.71 ± 3.82	24.71 ± 3.02	0.000•	1.000	NS
	Range	2 – 32	2 – 30			

Body Mass Index: BMI

Table (2): Risk factors distribution among the studied patients.

	Control group	TMZ group	Test value	P-value	Sig.
	No. = 100	No. = 100			
Smoking	56 (56.0%)	52 (52.0%)	0.322*	0.570	NS
Cannabis	9 (9.0%)	9 (9.0%)	0.000*	1.000	NS
HTN	67 (67.0%)	74 (74.0%)	1.178*	0.278	NS
DM	59 (59.0%)	55 (55.0%)	0.326*	0.568	NS
Family history	7 (7.0%)	11 (11.0%)	0.977*	0.323	NS
Dyslipidemic	30 (30.0%)	38 (38.0%)	1.426*	0.232	NS

DM: Diabetes Mellitus, HTN: Hypertension

Table (3): PTD, STEMI territory, culprit vessel, site of occlusion, thrombus burden, TIMI flow pre PPCI, KILLIP classification and coronary no reflow.

		Control group	TMZ group	Test value	P-value	Sig.
		No. = 100	No. = 100			
PTD (hours)	Median (IQR)	6.00 (4 - 10.5)	6.00 (4 - 9)	-0.909ǂ	0.363	NS
	Range	1 – 40	1 – 39			
STEMI	Anterior	62 (62.0%)	55 (55.0%)	1.009*	0.315	NS
	Inferior	38 (38.0%)	45 (45.0%)			
Culprit vessel	LAD	62 (61.0%)	55 (55.0%)	1.939*	0.585	NS
	LCX	11 (11.0%)	11 (11.0%)			
	RCA	27 (27.0%)	34 (34.0%)			
Site of occlusion	Distal	21 (21.0%)	14 (14.0%)	2.886*	0.236	NS
	Mid	48 (48.0%)	45 (45.0%)			
	Proximal	31 (31.0%)	41 (41.0%)			
Thrombus burden	3	9 (9.0%)	11 (11.0%)	0.556*	0.757	NS
	4	32 (32.0%)	35 (35.0%)			
	5	59 (59.0%)	54 (54.0%)			
TIMI flow pre PPCI	TIMI 0	73 (73.0%)	70 (70.0%)	0.239*	0.887	NS
	TIMI I	24 (24.0%)	27 (27.0%)			
	TIMI II	3 (3.0%)	3 (3.0%)			
Killip (class)	I	93 (93.0%)	92 (92.0%)	1.339*	0.720	NS
	II	5 (5.0%)	7 (7.0%)			
	III	1 (1.0%)	0 (0.0%)			

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	IV	1 (1.0%)	1 (1.0%)			
Post PCI no-reflow		18 (18.0%)	13 (13.0%)	0.954*	0.329	NS

PTD: Pain to door

Table (4): Baseline laboratory profile:

		Control group	TMZ group	Test value	P-value	Sig.
		No. = 100	No. = 100			
HGB (g/dl)	Mean ± SD Range	13.69 ± 1.40 10.5 – 16	14.13 ± 1.40 11.2 – 16.5	-1.229•	0.224	NS
TLC (thousands/cmm)	Mean ± SD Range	9.90 ± 2.68 5.9 – 18	9.35 ± 2.11 6.1 – 17	0.883•	0.381	NS
PLT (thousands/cmm)	Mean ± SD Range	266.03 ± 55.83 173 – 395	285.83 ± 57.23 187 – 411	-1.356•	0.180	NS
Creatinine (mg/dL)	Mean ± SD Range	1.04 ± 0.19 0.7 – 1.4	1.01 ± 0.20 0.6 – 1.5	0.599•	0.551	NS
LDL (mg/dL)	Mean ± SD Range	145.17 ± 39.74 70 – 237	150.47 ± 39.14 68 – 218	-0.520•	0.605	NS
HbA1c (%)	Mean ± SD Range	6.87 ± 1.42 5.1 – 11	6.68 ± 1.71 4.9 – 11.2	0.476•	0.636	NS

HBG: Haemoglobin, TLC: Total Leucocytic count, **PLT:** Platelets, **LDL:** Low density lipoproteins, **HBA1c:** Glycated hemoglobin

Table (5): ECG and Cardiac enzymes (baseline and after 24 hours):

		Control group	TMZ group	Test value	P-value	Sig.
		No. = 100	No. = 100			
Baseline						
CK-Total (units/L)	Median (IQR) Range	2055.5 (1622 – 2822) 638 – 5632	2250 (1296 – 2730) 464 – 5597	-0.007ǂ	0.994	NS
CK-MB (units/L)	Median (IQR) Range	252 (165 – 319) 96 – 763	264 (145 – 416) 55 – 802	-0.059ǂ	0.953	NS
Troponin I (ng/ml)	Median (IQR) Range	21.5 (14.4 – 29.2) 7 – 50	18.5 (15 – 22.5) 5.4 – 50	-1.176ǂ	0.239	NS
ST segment elevation on ECG (mm)	Mean ± SD Range	3.05 ± 1.59 1 – 6	3.03 ± 0.93 2 – 5	0.050•	0.961	NS
After 24 hours						
CK-Total (units/L)	Median (IQR) Range	1155.5 (751 – 1563) 408 – 4236	1042 (545 – 1293) 233 – 1922	-1.612ǂ	0.107	NS
CK-MB (units/L)	Median (IQR) Range	121 (89 – 154) 50 – 411	104 (54 – 142) 29 – 369	-1.412ǂ	0.158	NS
Troponin I (ng/ml)	Median (IQR) Range	9.2 (6.4 – 15) 3 – 24	8.1 (6 – 11.1) 2 – 22.5	-1.006ǂ	0.315	NS

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ST segment elevation on ECG (mm)	Mean ± SD Range	1.95 ± 0.94 0.5 – 4	1.28 ± 0.61 0.5 – 3	3.254•	**0.002**	**HS**

CK: Creatinine kinase, **CK-MB**: Creatinine kinase myocardial band, **ECG:** Electrocardiogram

Table (6): PCI technique and stent size:

		Control group	**TMZ group**	**Test value**	**P-value**	**Sig.**
		No. = 100	**No. = 100**			
PTCA once		59 (59.0%)	48 (48.0%)	2.432	0.119	NS
Balloon without inflation		95 (95.0%)	90 (90.0%)	1.802	0.179	NS
Stent diameter (ml)	Mean ± SD Range	2.98 ± 0.37 2.5 – 4	3.10 ± 0.33 2.5 – 3.5	-1.382•	0.172	NS
Stent length (ml)	Mean ± SD Range	28.40 ± 6.61 18 – 46	32.23 ± 9.04 15 – 48	-1.875•	0.066	NS

PTCA: Percutaneous transluminal coronary angioplasty.

Table (7): Echocardiographic assessment 1 day after PPCI:

1 day after PPCI		**Control group**	**TMZ group**	**Test value**	**P-value**	**Sig.**
		No. = 100	**No. = 100**			
EF % (Simpson)	Mean ± SD Range	42.07 ± 6.56 32 – 53	43.73 ± 6.06 34 – 54	-1.022•	0.311	NS
E/e'	Mean ± SD Range	10.93 ± 1.41 9 – 13	9.97 ± 1.92 6 – 13	2.221•	**0.030**	**S**
GLS (%)	Median (IQR) Range	-11.3 (-15.0 – -7.6) -18.5 – -5.80	-12.85 (-15.1 – -9.9) -17.8 – -8.0	-1.575ǂ	0.115	NS

EF: Ejection Fraction, **GLS**: Global Longitudinal Strain.

Table (8): Echocardiographic assessment after 1 month:

Follow up after 1 month		**Control group**	**TMZ group**	**Test value**	**P-value**	**Sig.**
		No. = 100	**No. = 100**			
EF % Simpson	Mean ± SD Range	44.93 ± 7.66 30 – 59	48.17 ± 7.05 35 – 58	-1.701•	0.094	NS
E/e'	Mean ± SD Range	10.87 ± 1.38 9 – 13	9.73 ± 1.80 7 – 13	2.736•	**0.008**	**HS**
GLS (%)	Median (IQR) Range	-13.75 (-17.2 – -7.3) -18.6 – 17.80	-15.85 (-18.0 – -15.0) -20.0 – -7.7	-2.647ǂ	**0.008**	**HS**

EF: Ejection Fraction, **GLS**: Global Longitudinal Strain.

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Table (9): Percentage of changes regarding baseline and after 1 day (ECG, cardiac enzymes and troponin) & after 1 day and after 1 month echocardiographic parameters in both groups:

% change of		Control group No. = 100	TMZ group No. = 100	Test value ǂ	P-value	Sig.
EF % (Simpson)	Median (IQR) Range	5.88 (3.85 – 8.51) -6.25 – 27.78	9.81 (6.98 – 12.82) 1.89 – 26.83	-2.507	**0.012**	**S**
E/E'	Median (IQR) Range	0 (0 – 0) -9.09 – 11.11	0 (0 – 0) -33.33 – 16.67	-0.074	0.941	NS
GLS (%)	Median (IQR) Range	13.22 (-6.9 – 30.93) -221.83 – 80.46	26.46 (9.55 – 35.79) -3.75 – 79.07	-1.730	0.084	NS
CK-total (units/L)	Median (IQR) Range	-45.49 (-52.93 – -39.52) -60 – 0	-52.71 (-60 – -50) -76.25 – -45.52	-3.844	**0.000**	**HS**
CK-MB (units/L)	Median (IQR) Range	-52.54 (-59.11 – -45.24) -69.86 – -17.2	-56.67 (-64.02 – -47.27) -77.63 – -43.59	-1.863	0.062	NS
Troponin I (ng/ml)	Median (IQR) Range	-55.29 (-57.89 – -52.24) -60.14 – -40	-55.16 (-58 – -52.16) -62.96 – -42.11	-0.288	0.773	NS
ST segment elevation on ECG (mm)	Median (IQR) Range	-33.33 (-40 – -25) -66.67 – 0	-66.67 (-66.67 – -50) -75 – -25	-4.777	**0.000**	**HS**

EF: Ejection Fraction, **GLS**: Global Longitudinal Strain, **CK:** Creatinine kinase, **CK-MB**: Creatinine kinase myocardial band, **ECG:** Electrocardiogram

Table (10): Clinical follow up of patients in both groups for 1 month:

	Control group No. = 100	TMZ group No. = 100	Test value	P-value	Sig.
Arrhythmia					
SVT	0 (0.0%)	0 (0.0%)	NA	NA	NA
AF	3 (3.0%)	2 (2.0%)	F	0.651	NS
VT	0 (0.0%)	0 (0.0%)	NA	NA	NA
Mortality	0 (0.0%)	0 (0.0%)	NA	NA	NA
Post MI Angina CCS III/IV	0 (0.0%)	0 (0.0%)	NA	NA	NA
Dyspnea NYHA III/IV			F	0.790	NS
III	4 (4.0%)	3 (3.0%)	0.148	0.700	NS
IV	2 (2.0%)	1 (1.0%)	0.338	0.561	NS

SVT: Supraventricular tachycardia, **AF:** Atrial Fibrillation, **VT:** Ventricular tachycardia, **MI:** Myocardial infarction, **CCS:** Canadian Cardiovascular Society, **NYHA:** New York Heart Association class

List of abbreviation:
ACS: Acute Coronary Syndromes.
AF: Atrial fibrillation.
AMI: Acute myocardial infarction.
ATP: Adenosine Triphosphate.
BID: Bis in die (Twice a day).
BMI: Body mass index.
CCS: Canadian Cardiovascular Society.
CK: Creatine Kinase.
CK-MB: Creatinine kinase myocardial band.
CVD: Cardiovascular disease.
DM: Diabetes Mellitus.
ECG: Electrocardiogram.
EF: Ejection Fraction.
GLS: Global longitudinal strain.

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HBA1c: Glycated hemoglobin.
HGB: Hemoglobin.
HTN: Hypertension.
IRA: infarct related epicardial artery.
LDL: low-density lipoproteins.
LVEDD: LV end-diastolic diameter.
LVESD: LV end-systolic diameter.
MACE: Major adverse cardiovascular events.
NR: No-reflow.
NSTEMI: Non-ST Segment Elevation myocardial infarction.
NYHA: New York Heart Association class.
PLT: Platelet.
PPCI: primary percutaneous coronary intervention.
PTCA: Percutaneous transluminal coronary angioplasty.
PTD: Pain to door.
STEMI: ST Segment Elevation myocardial infarction.
SVT: Supraventricular tachycardia.
TIMI: Thrombolysis in Myocardial Infarction.
TLC: Total leukocyte count.
TMZ: Trimetazidine.
VT: ventricular tachycardia.

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