



## Original Research Article

# ROLE OF TRIMETAZIDINE IN PREVENTING MYOCARDIAL INJURY IN PATIENTS UNDERGOING OFF PUMP CABG

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## ABSTRACT

**Background:** Off-Pump coronary artery bypass graft surgery (OPCABG) continues to be the main stay of surgical coronary revascularization for coronary artery disease in India. We evaluated the role of Trimetazidine (TMZ) in prevention of myocardial injury in patients undergoing OPCABG.

**Material and Methods:** A randomized prospective study was carried out to evaluate the efficacy of Trimetazidine in the prevention of myocardial tissue injury by measuring pre-operative and post-operative levels of cardiac troponin I (cTnI) at 8, 24 and 48 hours in patients undergoing elective OPCABG surgery. Seventy patients undergoing elective CABG were included in the study and were randomly (Covariate adaptive randomization) assigned to two groups, TMZ and Control (no TMZ) group. Thirty-five patients, received 80 mg of TMZ once daily in the pre-operative period (started a week before admission), were assigned to the TMZ group and thirty-five patients who did not receive TMZ, were assigned to the control group.

**Results:** In a study involving 150 enrolled cases, it was observed that 24 individuals experienced hypoglycemia within the first 72 hours of life. The occurrence of hypoglycemia observed in our study was 16%. Hypoglycemia occurred more frequently in neonates born to mothers under the age of 30; however, this association was not statistically significant. The incidence of hypoglycemia was observed to be higher in infants born via LSCS. In our research, we analyzed a total of 150 enrolled cases, of which 112 were classified as term, 30 as preterm, and 8 as post term. Our research identified 20 instances classified as small for gestational age (SGA). Among these, 13 were categorized as Term SGA, while 7 were identified as Preterm SGA.

**Conclusion:** Despite similar pre-operative baseline characteristics and pre-operative cTnI values, post-operative cTnI values showed a rising trend in both the groups, with the values peaking at 8 hours and thereafter following a gradual declining trend at 24 and 48 hours. However, the rise in cTnI levels, were significantly higher in the control group as compared to the TMZ group, in the post-operative period.

**Key Words:** TMZ – Trimetazidine, OPCAB - Off pump Coronary Artery Bypass, cTnI - Cardiac Troponin I, CABG - Coronary Artery Bypass Grafting.

## INTRODUCTION

Off-pump coronary artery bypass grafting (OPCAB) continues to flourish in India, and has been successfully adopted across the board in our country. In a country with limited resources and very poor health insurance cover, OPCAB significantly reduces the cost of CABG, which suits the need of the underprivileged population of a country suffering from an epidemic of coronary artery disease.<sup>[1]</sup> In spite of growing popularity there are few OPCAB publications from India.<sup>[2]</sup>

OPCAB is the main stay of surgical coronary revascularization, accounting for more than 80% of the coronary surgery, in India. Yadava, has reported a conversion rate of less than 1% and mortality of 1.6%, in over 5000 cases, states that this is an effective technique, provided it is adopted and practiced in spirit as well as letter.<sup>[3]</sup> OPCAB has been constantly evolving and MICS CABG is one of the latest addition to the armamentarium and has been rapidly gaining popularity in many centre's across the country.

However, myocardial ischemia and reperfusion injury may lead to reversible or irreversible myocardial injury and may manifest clinically as myocardial stunning, myocardial infarction manifesting as low cardiac output or arrhythmias. In patients dying soon after CABG, histological evidence of ischemia and reperfusion myocardial injury is detected in 25-45% postmortem evaluation. Therefore, myocardial preservation is of utmost importance in patients undergoing CABG.<sup>[4]</sup>

Of the various strategies available to minimize or prevent the extent of myocardial injury, pharmacological manipulation of pre-treatment with TMZ seems to exert a favourable effect.

Trimetazidine (1-[2,3,4-trimethoxybenzyl-piperazine dihydrochloride]) (TMZ) is a metabolic modulator, originally developed as an antianginal drug with coronary vasodilatory, cardio-protective 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 more energy efficient pathway of glucose oxidation, by selectively inhibiting mitochondrial long chain 3-ketoacyl coenzyme- A thiolase in the myocyte. As a result, TMZ decreases ischemic stress and improves cardiac performance due to direct cytoprotective effect on the myocardium and reduces myocardial necrosis without any negative inotropic effect and thus exerts a favourable effect on biomarkers of myocardial injury.<sup>[5]</sup> TMZ also reduces the formation of the oxygen free radicals, inhibits neutrophil infiltration, limits the accumulation of sodium and calcium in the cytoplasm of cardiac myocytes. The inhibition of apoptosis in cardiac myocytes is another possible mechanism, through which it exerts its cardio protective effect.<sup>[6]</sup>

When compared to CK-MB and other cardiac biomarkers, Troponin I or T has demonstrated nearly

absolute myocardial tissue specificity as well as high clinical sensitivity for myocardial injury or ischemia.<sup>[7]</sup> The majority of troponin is structurally bound in the contractile apparatus of the myofibril, but approximately 3-5% of troponin I is free in the cytoplasm. After damage to myocyte occurs, there is a biphasic rise in the serum troponin that corresponds to the initial release of free cytoplasmic troponin, followed by gradual dispersion of myofibril bound troponin complexes.<sup>[8]</sup> The sensitivity of troponin I is 69-82 % at 2-6 hours and achieves 100% between 6-12 hours after myocardial injury. The positive predictive value of troponin also increases with serial testing, improving from 29 % after injury to 89 % after 12 hours. Specificity of troponin I is in the order of

83-98 % with serial testing.<sup>[9]</sup>

### Aim

To assess the effect of oral TMZ in prevention or minimizing the extent of myocardial injury, by serial assessment of cTnI in patients undergoing elective off-pump CABG.

## MATERIALS AND METHODS

Seventy patients with preoperative coronary angiographic evidence of Triple vessel coronary artery disease (TVCAD) with or without left main coronary artery disease (LMCAD), with chronic stable angina, undergoing CABG from February 2019 to

February 2020 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.

### Group 1

35 patients received TMZ 80 mg, once daily, started one week prior to surgery and continued post operatively (TMZ group).

### Group 2

35 Patients did not receive TMZ in the pre-operative period (Control group).

Patients of both the groups received conventional treatment with anti-platelets, statins,  $\beta$ -receptor blockers, and nitrates. Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), were discontinued after admission in the pre-operative period in all the patients.

### Exclusion Criteria

Emergency CABG, Unstable Angina, Acute MI (less than 28 days duration), Chronic Kidney Disease, Concomitant valvular heart disease, Any patient requiring conversion to on pump for hemodynamic instability.

### End Points

The primary end point was a difference in post-operative cTnI levels, as compared to the pre-operative baseline values between the TMZ and control groups. The secondary end points were the

trend of rise, peak value reached and declining cTnI values in the post-operative period.

Venous blood samples for quantitative assessment of cTnI, was collected pre-operatively and at 8, 24 and 48 hours after completion of the procedure, and was measured using VITROSS5600 integrated system, Immunometric luminescent Immunoassay technique; Immunodiagnostic system, Ortho-Clinical diagnostics, USA, which involves the simultaneous reaction of cTnI present in the sample with biotinylated antibody (mouse monoclonal anti cTnI) and a Horseradish Peroxidase (HRP) labeled antibody conjugate (mouse monoclonal anti cTnI). The antigen antibody complex is captured by streptavidin on the wells and the bound HRP conjugate is measured by a Luminescent reaction. HRP conjugate bound is directly proportional to the concentration of cTnI present.

#### **Surgical Technique**

Standard anesthesia induction protocols were followed in both the groups

After standard median sternotomy, left internal mammary artery (LIMA) and saphenous vein grafts were harvested, Heparin (150-200 IU/kg) administered to achieve Activated clotting time (ACT) around 300s. In all cases LIMA was anastomosed to the left Anterior descending artery, and it was the first artery to be revascularized. Aortic top ends were done using aortic partial occluding clamp, depending on the number of vessels to be anastomosed, either sequentially or individually. The target coronary artery was stabilized using acrobat-i vacuum stabilizer system (Maquet), Intra coronary shunts - Clear view (Medtronic) was used for distal coronary anastomosis, proximal occlusion of target coronary artery was not done for any coronary artery in both the groups. At the end of the procedure, partial neutralization of heparin was done with protamine sulphate to achieve ACT of less than 200s. Inotropic support and Vasodilators were used accordingly to achieve desired hemodynamics in both the groups. IABP insertion and re-exploration was not required in any patient in either group.

#### **Sample size**

Sample size was calculated on the basis of 24 hour Trop I level in TMZ and control group using the formula for comparison of means discussed in 'A. Indrayan, Basic Methods of Medical Research' by putting SD's of Trop I as 0.31 in cases and 2.23 in control and a difference of means of the two SD's considered to be clinically significant.<sup>[10]</sup>

Considering 95% confidence level, 80% power of study, the minimum sample size was calculated to be 33 for each group. Adding 10% loss to follow up, it was taken to be 37, from which 35 were finally included in the study which had all the data figures

#### **Statistical Analysis**

All statistical analysis were performed using IBM SPSS Statistical software (IBM SPSS statistics, version 21.0; IBM SPSS, USA). Continuous variables are expressed as mean

SD and categorical variables as percentage. Unpaired students t test was carried out to compare quantitative values between the two groups and p value < 0.05 was taken as significance level.

## **RESULTS**

Seventy patients were included in the study and were randomly allotted to both the groups, thirty-five patients to each group. cTnI values were evaluated pre-operatively and serially at 8, 24 and 48 hours post-operatively in both the groups. cTnI values peaked at 8 hours, and thereafter followed a gradually declining trend at 24 and 48 hours. However, values were significantly higher in the control (no TMZ) group as compared to TMZ group. Despite similar pre-operative cTnI values in both the groups (TMZ vs control), cTnI values at 24 hours were 0.4303 vs 0.78823 ng/ml (p value = 0.001) and at 48 hours were 0.2848 vs 0.43289 ng / ml (p value = 0.034) with a statistically significant P value. However, at 8 hours cTnI values in TMZ vs control group was 0.6643 ng/ml vs 0.85977 (p value = 0.158), though the difference was statistically insignificant, the cTnI values were comparatively higher in the control group.

There was no emergency conversion to CPB, no patient required IABP insertion in the intra-operative or post-operative period and there were no mortalities in either group.

#### **Limitations**

Small sample size and power of study as 80 percent are the main limiting factors. Since the study included only patients with chronic stable angina undergoing elective surgery, role of TMZ in acute myocardial infarction undergoing emergency surgery needs to be evaluated further. Translation of the initial myo-protective effects in improvement of exercise capacity, improved or preservation of left ventricular ejection fraction and NYHA class needs to be evaluated further.

#### **Demographic characteristics and baseline medications**

The mean age of the patient population was 53.72 years in TMZ group and 54.48 years in the control group and 83 % were male in both the groups. Overall, 72 % had diabetes and 55 % had hypertension, and 32% had mild to moderate degree of chronic obstructive pulmonary disease. There was no significant difference in the TMZ and control group in terms of age, gender distribution, body surface area, prevalence of diabetes, hypertension. Both the groups were also comparable with regard to use of pre-operative cardiac medications. Left Internal mammary artery was used in all the patients in both the groups. Average number of grafts in both the groups were similar, 3.2 in the TMZ and 3.1 in the control group. Average pre-operative left ventricular ejection fraction in both the groups were similar.

Detailed demographics in both the groups were comparable as given in Table 1.

**Table 1: Pre-operative characteristics of patients**

	TMZ	Control (Non TMZ)
Age (years)	40-74 (53.72)	45-70 (54.48)
Gender M/F	30/5	30/5
LVEF	4511.2	4610.4
Risk Factors		
a. Hypertension	21	18
b. Diabetic	25	26
c. COPD	12	11
Use of LIMA	35	35
No. of vessels grafted	3.2	3.1
Body Surface area	1.6574	1.6174

**Table 2: Measurement of cTnI values**

	TMZ (n=35) Mean □ SD	No TMZ (n=35) Mean □ SD	P value
T1 : Pre-Op	0.0798 □ 0.1487	0.0998 □ 0.1837	0.618
T2 : 8 Hours	0.6643 □ 0.6329	0.85977 □ 0.5068	0.158
T3 : 24 Hours	0.4303 □ 0.4743	0.78823 □ 0.4182	0.001
T4 : 48 Hours	0.2848 □ 0.3266	0.43289 □ 0.2405	0.034

**Line chart 1: X axis – cTnI values in ng / ml Y axis – Time duration in hours**

## DISCUSSION

There are only few studies evaluating the protective role of TMZ in patients undergoing off-pump coronary artery bypass graft surgery (OPCABG). Considering the protective effect of TMZ in patients undergoing percutaneous transluminal coronary angioplasty (PTCA), the use of TMZ in patient undergoing surgical revascularization, seems justified.<sup>[11]</sup> TMZ has been shown to reduce myocardial injury during conventional CABG.<sup>[12]</sup> TMZ also acts as an anti-ischemic agent and functions by inhibiting fatty acid Beta oxidation and increasing glucose oxidation, increasing the antioxidant capacity and protects against oxygen free radical induced toxicity. It also counteracts calcium overload and reduces area of necrosis. Chronic treatment with trimetazidine has also shown to protect against ischemia-induced arrhythmias and to reduce myocardial infarct size.<sup>[13]</sup> This myocardial protecting effect of the drug may be due to its role as a free radical scavenger.

In this study, treatment with trimetazidine (35 mg twice daily for one week) was started in the pre-operative period and continued post-operatively. The mean pre-operative cTnI levels were similar in both the groups. In the Post-operative period cTnI levels were measured at 8 hours, 24 hours, and 48 hours. cTnI levels were significantly lower in the TMZ group. Isken et al investigated the effect of Pre-operative use of TMZ on the reduction of oxidative stress during CABG.<sup>[15]</sup> Long term use of Trimetazidine MR (modified release) improves LV function and exercise tolerance. Results of meta-analysis of six RCT, published by Heil et al, 2015, showed significantly lower post-operative levels of CK, CK-MB, cTnT and cTnI in the TMZ group.<sup>[16]</sup>

## CONCLUSION

The study evaluated the protective role of TMZ on myocardial injury in patients undergoing OPCABG, by serial assessment of cTnI, as a biochemical marker of myocardial injury. Significantly lower levels were found in the TMZ group as compared to the control group undergoing OPCABG. Thus preoperative TMZ therapy appears to have a positive effect on myocardial preservation undergoing OPCAB. Meta-analysis of Gao et al showed long term use of TMZ to be associated with increased exercise tolerance, reduction in NYHA class, improved left ventricular ejection fraction, a reduced rate of cardiovascular events, hospitalizations and reduction in overall mortality.<sup>[17]</sup> With a well known mechanism of activity, the use of TMZ in patients undergoing surgical revascularization seems to be completely justified.<sup>[18]</sup> Thus it can be concluded that TMZ is a unique and undervalued anti-anginal agent, an attractive and potential alternative to conventional agents, and it can be used as a monotherapy or combination therapy with conventional anti-anginal agents.<sup>[19]</sup> However recommendations over long term use needs to be further evaluated.

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