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Original Research Article

Effects of Modified-release Trimetazidine as an Adjunct to Standard Treatment in Dilated Cardiomyopathy

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Conflict of interest: Nil

Abstract

Background: Several clinical studies have reported numerous benefits of trimetazidine, an anti-ischemic agent, in ameliorating symptoms associated with cardiac dysfunction. Our study determined efficacy of trimetazidine as an adjunct to standard medical treatment in a population of Indian patients with dilated cardiomyopathy.

Methods: Forty-five patients with ischemic dilated cardiomyopathy with previous history of acute myocardial infarction and/or documented coronary artery disease were enrolled in the study. Patients were included if the dilated left ventricular internal dimension-diastole (LVIDd) was >57 mm and the left ventricular ejection fraction (LVEF) was ≤30%. All patients received trimetazidine 35 mg modified-release formulation twice-daily and standard medical therapy for 24 weeks.

Results: After 6 months, there was a significant increase in mean LVEF values by 7.1% (29.78 ± 05.11 vs. 31.89 ± 04.56, P=0.002) compared with pre-treatment values. Moreover, there was a significant increase in mean six-minute walk test scores by 7.9% (314.55 ± 65.72 vs. 339.40 ± 76.94, P=0.001). Furthermore, a significant decrease was noted in mean plasma brain natriuretic peptide levels (pro-BNP) by 16.9% from pre-treatment levels (1010.09 ± 589.03 vs. 839.55 ± 611.01, P=0.001). In addition, a nonsignificant decrease (0.4%) was observed in mean LVIDd values compared with pre-treatment values.

Conclusion: Trimetazidine is beneficial in Indian patients with ischemic dilated cardiomyopathy with significant improvements in symptoms (LVEF), functional status (6-minute walk test), and inflammation (pro-BNP levels).

Keywords: Dilated cardiomyopathy, trimetazidine, LVEF, observational study

Introduction

Dilated cardiomyopathy (DCM) is characterized by ventricular dilation and systolic dysfunction of one or both ventricles. It is a primary cardiomyopathy seen in approximately 25% of all patients presenting with cardiac failure. Main features of DCM include increasing systolic and diastolic ventricular volumes with decreasing left ventricular ejection fraction (LVEF) below 40%.[1] Despite considerable advances in therapeutics, DCM continues to be a leading cause of morbidity and mortality in developed countries. With a projected prevalence of 1:2500 in the United States, DCM constitutes the third most common cause of cardiac failure and the most frequent reason for heart transplantation.[2] However, the prevalence of DCM is considerably higher in underdeveloped and tropical countries than in developed countries.[1]

Therapeutic classes of drugs that are used for management of DCM include angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and beta-blockers.[1] Trimetazidine (TMZ) is a key metabolic modulator that inhibits the long-chain mitochondrial enzyme 3-ketoacyl coenzyme A thiolase, a key enzyme in the beta-oxidation pathway.[3] This subsequently leads to inhibition of myocardial fatty acid uptake and oxidation and consequent stimulation of glucose oxidation.[4] Hence, TMZ acts by improving myocardial substrate utilization with a shift of energy production from free fatty acids (FFAs) to the more energy-efficient pathway of glucose oxidation.[3]A hypo perfused myocardium benefits from a shift towards glucose oxidation because compared with fatty acids, a greater number of moles of adenosine triphosphate (ATP) produced per mole of oxygen (~12%) are consumed for glucose. This results in improvement in both left ventricular systolic and diastolic function in patients with DCM.[5–9] TMZ has been seen to act as an anti-ischemic agent without exerting an effect on myocardial oxygen consumption, coronary blood flow, contractility, blood pressure, or heart rate.[7] Therefore, unlike conventional drugs, TMZ has no significant negative inotropic or vasodilatory properties at rest or during exercise; hence, it can be excellently combined with conventional pharmacotherapy, used as add-on therapy, as well as substitution therapy when conventional drugs are not tolerated.[10]

Several short- and long-term clinical studies have reported numerous benefits of TMZ in patients with DCM, including symptomatic relief, improvement of clinical status, reduction of ventricular volume, improvement of LV systolic and diastolic function, anti-inflammatory action resulting in production of low C-reactive protein (CRP) levels, and antioxidant action, with subsequent improvement of endothelial dysfunction.[9,11] In a meta-analysis that included 19 randomized controlled trials (RCTs) involving 994 patients with chronic heart failure, TMZ was seen to improve clinical symptoms and cardiac function, reduce hospitalization for cardiac causes, and decrease serum levels of brain natriuretic peptide (BNP) and CRP.[12]

Given the unmet need for treatment of DCM in Indian patients, the promising pharmacological and pharmacodynamic profile, and the demonstrated treatment potential of TMZ, this study sought to evaluate its effects as an adjunct to standard medical treatment and compare these effects before and after treatment.

Methods

Study design

This was a prospective, open-labelled, single-centered, comparative,

observational, phase 4 study. All patients who fulfilled the inclusion criteria were enrolled in the study to receive TMZ (35 mg modified-release formulation twice-daily) following standard medical treatment for DCM. The planned duration of treatment for each patient was approximately 24 weeks.

Patient enrolment

All consecutive stabilized adult patients with decompensated heart failure and receiving standard medical therapy who attended the intensive cardiac care unit (ICCU) and outpatient department (OPD) of the igims for routine medical care were enrolled in the study. This included patients with previous history of acute myocardial infarction and/or documented coronary artery disease on previous coronary angiography (CAG), idiopathic cardiomyopathy, or dilated left ventricular internal dimension-diastole, LVIDd >57 mm, and LVEF ≤30%. Patients with valvular cardiomyopathy, renal impairment, chronic obstructive pulmonary disease, or other severe comorbid conditions, with known active neoplasms, or an orthopedic or neurological illness that could limit the ability to exercise were excluded.

All patients provided written informed consent prior to enrolment. This study was conducted in accordance with principles of the Declaration of Helsinki and in full conformity with relevant regulations, including guidelines of the International Conference of Harmonisation Good Clinical Practice (ICH-GCP).

Study of left ventricular function

All patients underwent transthoracic echocardiogram following guidelines of the American Society of Echocardiography. Parasternal and apical views were used to calculate dimensions and evaluate the global and regional LV function. Various 2D echocardiographic and Doppler indices, including left ventricular end-diastolic dimensions and volumes (LVEDDs, LVEDVs), left ventricular end-systolic dimensions and volumes (LVESDs, LVESVs), LVEF, stroke volume (SV), and fractional shortening (FS) were recorded. LV dimensions were obtained from the parasternal long-axis view and LV volumes from apical four- and two-chamber views by using the modified Simpson's rule, from which ejection fraction was automatically calculated as the difference between end-diastolic volume and end-systolic volume normalized to end-diastolic volume.

Image analysis

All echocardiograms were performed using the iE33 xMATRIX Echocardiography System (Philips, Amsterdam, Netherlands).

Endpoints

The primary endpoint was improvement in LVEF and other echocardiographic parameters at 6 months. Secondary outcomes included evolution of patients' functional status (New York Heart Association [NYHA] class and 6-minute walk test) and change in highly sensitive plasma C-reactive protein (hs-CRP) and pro-brain natriuretic peptide (pro-BNP) concentrations. Patients' functional status (NYHA class) and exercise tolerance (6-minute walk test) were recorded at enrolment and at 6 months. Plasma hs-CRP and pro-BNP levels were measured at baseline and at 6 months. Severity of adverse events (AEs) was assessed by the investigator and categorized into mild (barely noticeable), moderate (patient uncomfortable), and severe (severe discomfort).

Statistical analysis

All values are given as mean ± SD or percentages where appropriate. Differences in mean values between baseline (pre-) and post treatment values

were assessed using the two-tailed Student's t-test. Categorical variables were analyzed using the Chi-square test or Fisher's exact test. All calculated P values are two-tailed and considered significant when <0.05. The sample size required to determine the difference between groups was calculated based on the historical size of the cohort. At 80% power and by the use of a two-sided confidence interval (CI) of 95%, assuming a 10% dropout rate, a minimum of 45 patients were needed to be included per group.

Results

A total of 45 patients with heart failure post stabilization were included in the study. The mean age of patients was 47.36 ± 11.22 years and 73.3% were men. Baseline characteristics of patients are presented in **Table 1**.

Table 1: Baseline and demographic characteristics of patients

Characteristic	
Age, mean ± SD, n=45	47.36 ± 11.22
Female, n(%)	12 (26.7)
Heart rate (beats/min)	92.23 ± 07.60
Blood pressure (mm Hg)	103.18 ± 07.39
Hemoglobin (g/dL)	11.92 ± 01.79
Creatinine (mg/dL)	1.17 ± 0.15
Blood sugar levels (mg/dL)	124.57 ± 38.82

Values are presented as mean ± SD unless specified
HDL: high density-level cholesterol, LDL: low density-level cholesterol, NS: not significant, SD: standard deviation, TMZ: trimetazidine

At before treatment, the mean creatinine was 1.17 mg/dL; after treatment, this value showed an insignificant increase by 1.7% from pre-treatment levels (**Table 1**).

At 6 months, a statistically significant increase was noted in mean LVEF values after treatment by 7.1% (29.78 ± 05.11 vs. 31.89 ± 04.56, mean difference: 2.11 ± 04.46, P=0.002, n=45) (**Figure 1**).

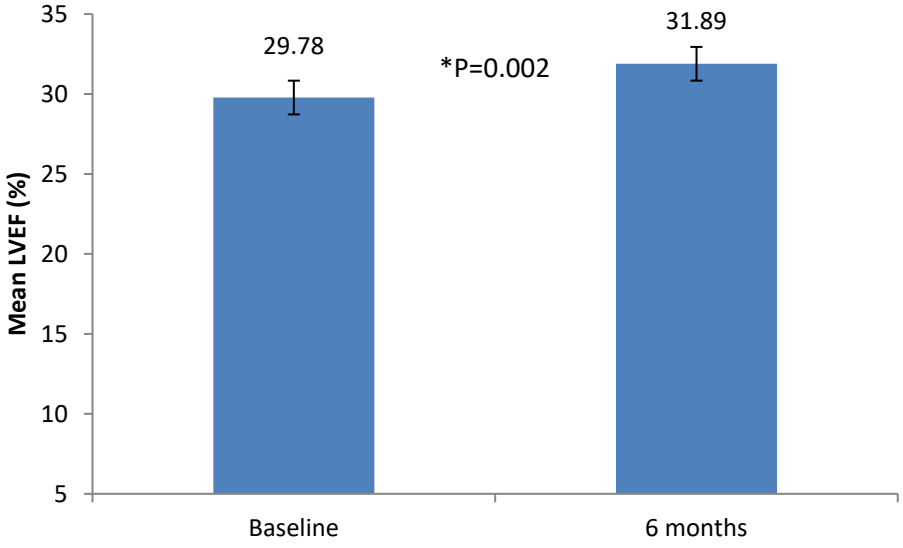

Figure 1: Changes in mean left ventricular ejection fraction (LVEF) at baseline and at 6 months

In addition, a significant increase was noted in mean 6-minute walk test scores by 7.9% after treatment with TMZ (314.55 ± 65.72 vs. 339.40 ± 76.94, mean difference: 24.86 ± 47.51, P=0.001, n=42) (**Figure 2**).

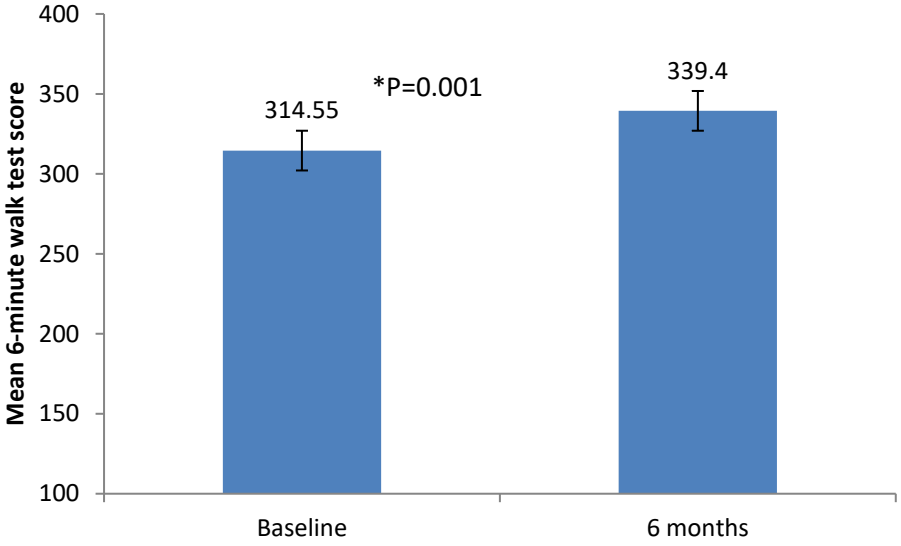

Figure 2: Changes in mean 6-minute walk test scores at baseline and at 6 months

On the other hand, a significant decrease was noted in mean BNP levels by 16.9% from pretreatment levels (1010.09 ± 589.03 vs. 839.55 ± 611.01, mean difference: -170.54 ± 299.90, P=0.001, n=42) (**Figure 3**).

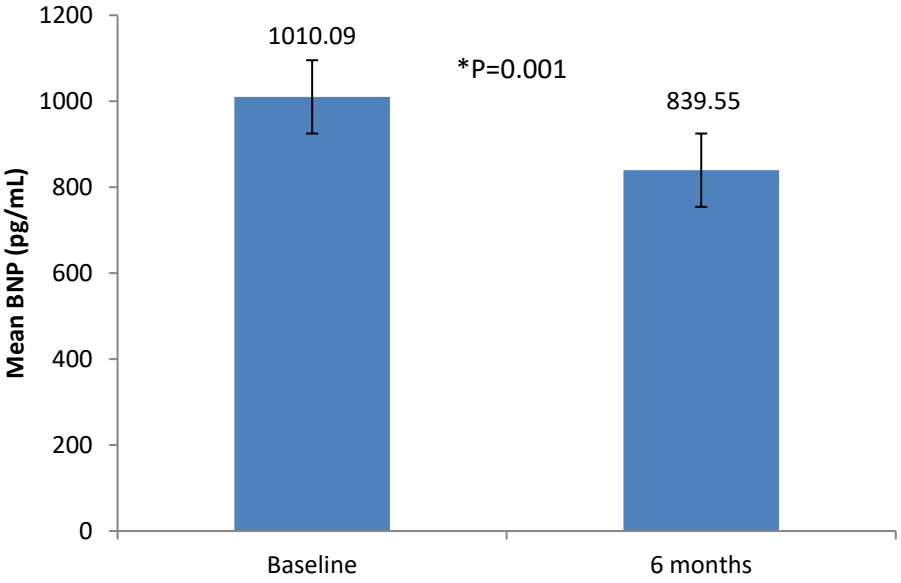

Figure 3: Changes in mean brain natriuretic peptide (BNP) levels at baseline and at 6 months

Moreover, a nonsignificant decrease (0.4%) was seen in mean LVIDd values compared with pretreatment values (**Figure 4**).

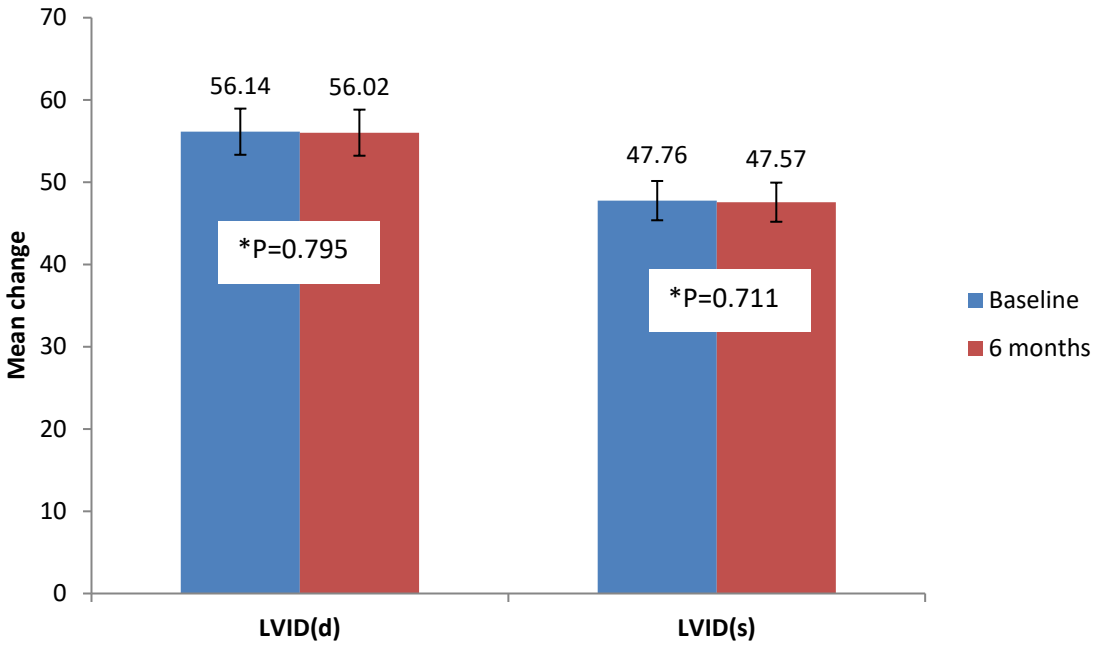

Figure 4: Changes in mean left ventricular internal dimension-diastole (LVID [d]) at baseline and at 6 months

Furthermore, a nonsignificant decrease in mean levels of triglycerides by 6.6% was observed during the study. Interestingly, there was a significant decrease in mean LDL levels after treatment by 11.2% compared with pre-treatment levels (84.17 ± 26.80 vs. 74.75 ± 20.54, mean difference: -9.42 ± 24.14, P=0.025); a nonsignificant increase by 4.2% in mean HDL levels and a significant decrease in the mean heart rate by 3.9% were also noted compared with pre-treatment values (92.23 ± 07.60 vs. 88.64 ± 07.42, mean difference: -3.59 ± 06.55, P=0.001) **(Figure 5)**.

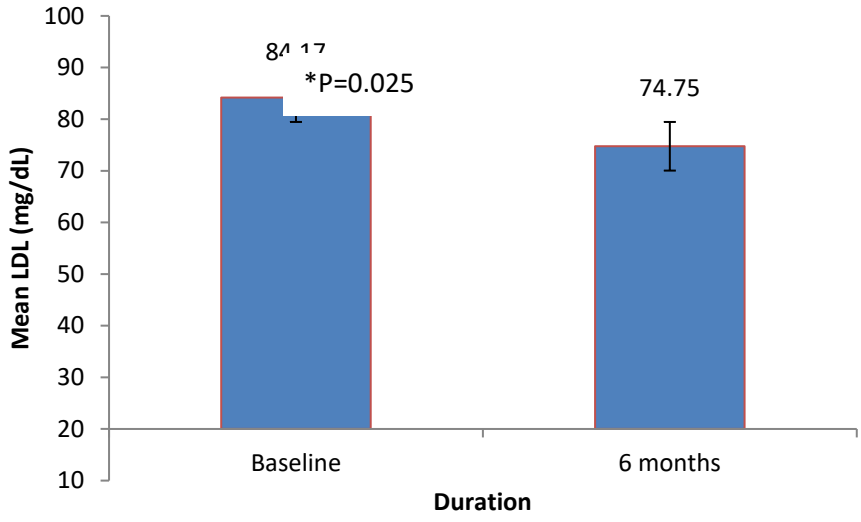

Figure 5a: Changes in mean LDL levels from baseline and at 6 months

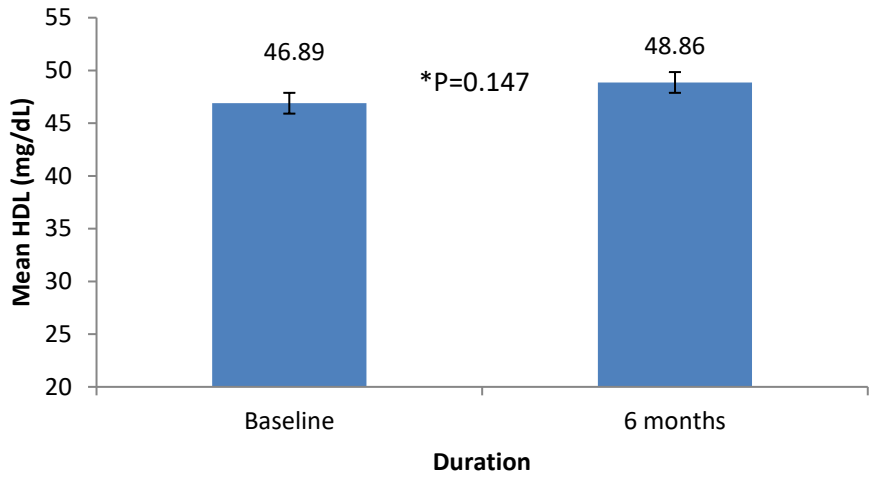

Figure 5b: Changes in mean HDL levels from baseline and at 6 months

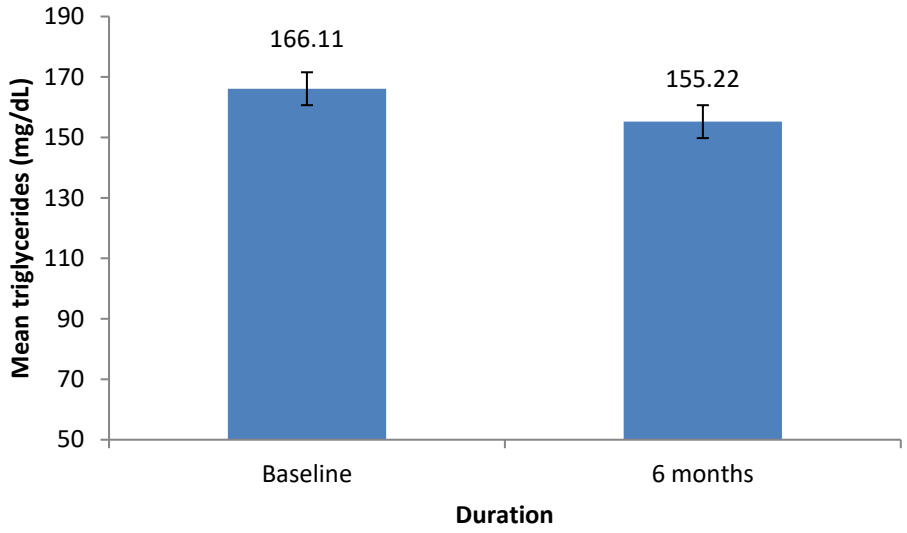

Figure 5c: Changes in mean triglyceride levels from baseline and at 6 months

Discussion

The present study demonstrated that addition of TMZ to standard medical therapy for DCM improves patients' symptoms and functional status, including LVEF and performance on 6-minute walk test. Although nonsignificant, there was improvement in the LV dimension and systolic function. Reduction in levels of BNP, which is a marker of intrinsic cardiac dysfunction, following treatment with TMZ demonstrates its efficacy in amelioration of symptoms.

In various RCTs that have been published to date, TMZ has been reported to demonstrate significant improvement in heart failure,[9] left ventricular end-diastolic volume,[6] wall thickness score index,[13] wall motion score index at rest,[7] peak oxygen volume,[13] and inflammation assessed by plasma levels of CRP.[9,14] Functional and echocardiographic observations in this study are similar to those observed in previous short- and long-term studies and hence confirm and support these findings.

In an RCT that assessed the long-term (24 months) effect of TMZ (20 mg thrice-daily) on myocardial perfusion in 200 patients aged 54.7 ± 12 years with ischemic left ventricular dysfunction and multivessel coronary artery disease, a significant decrease was reported in the frequency of anginal episodes per week (3.9 vs. 5.7, P<0.01) compared with placebo in 91% of patients. In addition, TMZ significantly lowered weekly nitroglycerin (glyceryl trinitrate) tablet consumption after 24 months. Moreover, a significant reduction was noted in summed stress and rest scores as well as ejection fraction of 23% (P<0.001) without significant changes in hemodynamic parameters. However, most importantly, TMZ resulted in reduction of mortality by 30%.[15]

In a single-center, open-labelled RCT, 61 patients with chronic heart failure were randomized to either receive TMZ (20 mg thrice-daily) in combination with their conventional treatment or were made to continue their usual therapeutic regimen for 4 years. Adjunctive TMZ with conventional treatment significantly reduced all-cause mortality by 56% and heart failure hospitalization by 47% and significantly improved LVEF and patient functional status, as was demonstrated by an increase in 6-minute walk test scores.[14]

Another RCT reported improvement in LVEF by 9.3% as well as cardiac volumes in patients with severe ischemic cardiomyopathy following a 6-month therapeutic regimen with TMZ.[5] Three other RCTs, including a study involving Bangladeshi patients, have reported a significant improvement in TMZ-induced clinical status and ejection fraction in diabetic patients with ischemic cardiomyopathy.[6,16,17] While Rosano et al. reported an increase in LVEF by 5.4% (P<0.05) in patients with diabetic ischemic cardiomyopathy following treatment with TMZ,[16] we observed an improvement by 7.1% in our study; however, the patients in our study demonstrated a mean blood sugar level of 124.57 ± 38.82 and, hence, can be considered as prediabetic.

In another RCT by Di Napoli et al., 6-month (24 weeks) TMZ treatment (20 mg thrice-daily) significantly improved exercise tolerance (P<0.01) and significantly reduced plasma BNP levels (P<0.001) in patients with ischemic cardiomyopathy.[18] Similar findings were noted in our study as well. TMZ was also reported to be beneficial in elderly patients with DCM (mean age: 78 years) as it improved their clinical condition and quality of life on both social and physical (MacNew Quality of Life) scales.[19]

Beneficial effects of TMZ are due to its unique mechanism of action that protects the myocardial cell against necrotic and apoptotic cell death. Preservation of LVEF following treatment with TMZ is due to the maintenance of integrity of cell membranes and mitochondrial structure and function.[20] Improvement in contractility and microvascular function may be due to an increase in glucose oxidation and subsequent resynthesis of glycolytic ATP, both of which are induced by TMZ. After TMZ treatment, there is an increase in energy metabolism in hibernated myocardial cells that leads to improvement in contraction. Additional benefits of TMZ include anti-inflammatory and antioxidant effects.

This is an important observational study involving Indian patients on use of TMZ for treatment of DCM.[22] A major limitation of this study was a very small sample size consisting of only 45 patients and a relatively short study duration. Hence, additional studies involving a larger sample size of Indian patients and conducted for longer duration are warranted to strengthen the findings reported in this study.

Conclusions

Adjunctive treatment with modified-release TMZ (30 mg twice-daily) concurrently with standard medical treatment for 24 weeks significantly improved symptoms (LVEF), functional status (6-minute walk test), and inflammation (pro-BNP levels) in Indian patients with DCM. Trimetazidine could be an effective add-on treatment option for patients who have inadequately controlled angina despite conventional antianginal drugs.

Conflicts of interest

<<Please disclose>>

Acknowledgments

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