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Original Article

Effects of sustained-release trimetazidine on chronically dysfunctional myocardium of ischemic dilated cardiomyopathy – Six months follow-up result

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ABSTRACT

Background: Ischemic cardiomyopathy is a growing burden in third world countries. So far, benefits of trimetazidine in this group of patients have been suggested by clinical trials mainly conducted in Europe. We evaluated the effect of trimetazidine on ischemic dilated cardiomyopathy in our population.

Methods and results: 98 patients (aged 58.5 ± 9.2 years), admitted with decompensated heart failure with previous history of MI and/or documentation of significant CAD with previous CAG, were chosen for the study. Patients were randomized into two groups – one provided with trimetazidine 35 mg sustained released tablet, twice daily and the other with a placebo, along with other conventional medications. Patients were expected to have dilated LV (LVIDd > 57 mm) and left ventricular ejection fraction (LVEF) ≤40%. After 6 months, significantly higher number of patients in trimetazidine group was in NYHA class I (22% vs. 8%, $p = 0.03$) and class II (56% vs. 34%, $p = 0.01$); higher number of patients in placebo group was in NYHA class III class IV. Anginal episodes and use of sublingual nitrate per week were significantly lower in the trimetazidine group. Left ventricular diastolic dimension (59.7 ± 5.2 vs. 65.1 ± 6.1, $p = 0.001$) was significantly different in the two groups as was the increase of LVEF (11% vs. 5.6%, $p = 0.001$). Hospitalization for worsening heart failure was significantly lower in trimetazidine group (13 vs. 22, $p = 0.047$).

Conclusion: Trimetazidine seems to be beneficial in patients with ischemic dilated cardiomyopathy even in South Asian population and larger scale study with extended follow-up is needed.

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1. Introduction

Although there are considerable advances in therapeutics, heart failure remains a leading cause of mortality and morbidity in developed[1] and increasingly in developing countries.[2] It has a high fatality rate, with 5 years mortality in more than 50% cases, which exceed that of many cancers.[3] The prognosis worsens with advancement of heart failure and the mortality of patients with New York Heart Association (NYHA) class IV is as high as 50% per year.[4]

Trimetazidine (TMZ) (2,3,4-trimethoxybenzyl-piperazine dihydrochloride) has been reported to exert antiischemic properties without affecting myocardial oxygen consumption and blood supply.[5] Additional studies have shown that TMZ may also be beneficial in patients with heart failure, in terms of LV function preservation and symptoms control.[6–10] It is a metabolic modulator that is so far known to inhibit a key enzyme in fatty acid oxidation – the mitochondrial long-chain 3-ketoacyl coenzyme A thiolase – and shifts cellular energy substrate reference from fatty acids to glucose oxidation.[11] A shift toward glucose oxidation is likely to benefit hypoperfused myocardium, because the number of moles of ATP produced per mole of oxygen consumed is approximately 12% higher for glucose than of fatty acids. As a result, both left ventricular systolic function and diastolic filling are improved in patients with ischemic and diabetic cardiomyopathy and idiopathic dilated cardiomypathy.[6,8,12] The beneficial effect of this agent has also been attributed to preservation of the phosphocreatine (PCr) and adenosine triphosphate (ATP) intracellular levels[13] and reduction of cell acidosis,[14,15] calcium overload,[15] and free-radical-induced injury caused by ischemia.[16] It also improves endothelial dysfunction directly by decreasing nitric oxide inactivation through decreased production of lipid peroxidation,[17–19] and indirectly through enhanced LV function.[12,20,9] Recently the evidence for another important property of the drug is observed. TMZ improves radial artery endothelium-dependent relaxation in chronic heart failure.[18] This effect is correlated with decreased plasma levels of lipid-free radicals, suggesting an antioxidant action.

So far, many short- and long-term studies revealed several benefits of TMZ in ischemic cardiomyopathy patients, including symptomatic relief, improvement of clinical status, reduction of ventricular volume and improvement of LV systolic and diastolic function, anti-inflammatory action producing low CRP level, and antioxidant action resulting in improvement of endothelial dysfunction. The purpose of our study is to evaluate the effects of TMZ in the Bangladeshi patients' population with ischemic dilated cardiomyopathy, which has not been tested yet.

2. Methods and enrolment of patients

Patients admitted in the National Institute of Cardiovascular Diseases with decompensated heart failure were taken for study. Among them, those who had previous history of acute myocardial infarction, revealed from history and previous documentation, were considered for the study. Patients having a history of previous coronary angiogram with documented significant coronary artery disease with or without coronary revascularization were also enrolled in this study. Patients planned for revascularization were excluded. Informed written consent was taken before enrolment. A total 120 patients were screened and finally 102 patients fulfilled the inclusion and exclusion criteria. Of them, the ischemic nature of cardiomyopathy was demonstrated by CAG with significant stenosis of at least one major coronary artery in only 25 patients and the rest were diagnosed by history and previous documentation of acute myocardial infarction. After initial stabilization in the hospital, they were kept under observation at home for 1 month for more stabilization, and during that time at home, 4 patients developed worsening symptoms and were readmitted and were excluded from the study. Finally, 98 patients were enrolled in the study. Baseline examination and investigations were done in that time. Enrolled patients should have dilated LV (LVIDd $>$ 57 mm) and LVEF $\leq$ 40%. Patients with dilated cardiomyopathy without documentation of myocardial infarction or coronary significant lesion in CAG were excluded. Patients with valvular cardiomyopathy, renal impairment, COPD, and other severe comorbid conditions were excluded from the study (Table 1).

Table 1 – Inclusion and exclusion criteria.

Inclusion criteria
1. Patients admitted with decompensated heart failure later stabilized
2. With previous history of acute myocardial infarction and/or documented coronary artery disease on previous CAG
3. Not planned for revascularization
4. Dilated LV (LVIDd $>$ 57 mm) and LVEF $\leq$ 40%
Exclusion criteria
1. Idiopathic dilated cardiomyopathy
2. Without documentation of myocardial infarction or coronary significant lesion in CAG
3. Valvular cardiomyopathy
4. Patients with renal impairment,
5. COPD
6. Severe comorbid condition

2.1. Study design

The study design was double blinded, randomized, parallel, placebo-controlled. After a baseline evaluation of all inclusion and exclusion criteria, patients entered a run-in phase up to 4 weeks, at the end of which patients underwent a baseline echocardiogram and were then randomized to receive either TMZ (35 mg sustained-release preparation b.i.d.) or matching placebo (b.i.d.) for 6 months. The transthoracic echocardiogram was repeated at the end of the treatment period. Patients received a diary card to document the occurrence of episodes of chest pain and use of nitroglycerin spray.

2.2. Study of left ventricular function

All patients underwent transthoracic echocardiogram following the guidelines of the American Society of Echocardiography, using the parasternal and the apical views to calculate dimensions and evaluate global and regional left ventricular function.

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