Original Article

EFFECT OF TRIMETAZIDINE ON FUNCTIONAL CAPACITY IN DIABETIC PATIENTS WITH LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

Imran Waheed[a*], Zeeshan Hassan[b], Moazzam Ali Naqvi[b], Masood Ali Akbar[b], Ahmad Noeman[b], Muhammad Abu bakar Mirza[b]

[a] Department of Cardiology, Government Khawaja Muhammad Safdar Medical College/ Allama Iqbal Memorial Teaching Hospital , Sialkot.
[b]Department of Cardiology, Punjab Institute of Cardiology, Lahore
* Corresponding author: cardiovascularpic@gmail.com

Submission Date : 11-10-2019
Revision Date: 01-11-2019
Publication Date: 25-12-2019

Author's Contribution

IW:Conducted the study and wrote the article. ZH: Helped in review the article. MAN: Re-arranged data and corrected article. MAA: Tables and figures. AN and MABM made corrections and did the proof reading.

All authors declare no conflict of interest.

This article may be cited as: Waheed I, Hassan Z, Naqvi MA, Akbar MA, Noeman A, Mirza MAB. Effect of trimetazidine on functional capacity in diabetic patients with left ventricular systolic dysfunction . (J Cardiovasc Dis 2019;15(4):99 - 103)

ABSTRACT

INTRODUCTION:Varying approaches have been adopted in past to study the effect of different pharmacological interventions on functional capacity of the heart in patients with left ventricular systolic dysfunction. The role of Trimetazidine has also been evaluated in patients with angina and heart failure but there is paucity of research on the impact of Trimetazidine on functional capacity of patients with left ventricular systolic dysfunction and metabolic syndrome in previous literature. The purpose of the study was to assess the efficacy of Trimetazidine therapy on functional capacity of patients with left ventricular systolic dysfunction.

MATERIAL AND METHODS:This was observational open labeled study conducted in Department of Cardiology, Government Khawaja Muhammad Safdar Medical College, Sialkot from 1st June 2018 to 31st August 2018. A total number of 200 diabetic patients with left ventricular systolic dysfunction were included in the study while patients with valvular and congenital heart disease were excluded from the study. Informed consent was taken. Left ventricular systolic dysfunction was diagnosed and graded on Echocardiography and LVEF was calculated. At the beginning, the basal Duke Activity Status Index (DASI) score (Total Score is 58.2 with METS of 9.8), VO_2 and METs was calculated in all the study cases. All patients were given sustained release Trimetazidine 70 mg in divided doses on daily basis for two months at the end of which DASI score, VO_2 and Mets were again calculated as final parameters along with reassessment of LV systolic dysfunction. All the collected data was subjected to statistical analysis and results were analyzed at the end of the study.

RESULTS: 120 (60%) patients had moderate LV systolic dysfunction out of which 40 patients showed improved LV function at the end of drug therapy with 70 mg of Trimetazidine while cases with LVEF ranging between 25-30% or severe LV systolic dysfunction revealed similar improvement. An improvement in NYHA Class was observed pre-trimetazidine and post-trimetazidine therapy. NYHA Class improvement was seen from 73 (36.5%) to 41 (20.5%) in Class III while Class IV revealed much more improvement from 127 (63.5%) to 73(36.5%). DASI score improved from basal level of 26.30 to a final score of 41.76 with an overall improvement in METS from 5.94 to 7.8 at completion of the study

CONCLUSION: In our study population drug therapy with sustained release Trimetazidine 70 mg in divided doses daily has shown significant improvement in functional capacity of the

patients in terms of VO_2, METS and DASI score. It may be concluded that this drug may improve symptomatic outcomes in patients with moderate to severe LV systolic dysfunction.

(J Cardiovasc Dis 2019;15(4):99 - 103)

INTRODUCTION:

VO_2 is defined as the maximum volume of Oxygen that the body of a human being can consume during intense whole body exercise . VO_2 max is the point at which Oxygen consumption is at its peak and plateaus i.e. an individual's maximal aerobic capacity. VO_2 is a parameter with a resting as well as a plateau or maximum value. Its rise or fall can be a very useful determinant especially in patients with LV systolic dysfunction and Low exercise functional capacity measured in terms of METS which can be easily calculated with the availability of DASI score of the patient and VO_2 at rest and after exercise or a metabolic drug therapy. A lot of data is available on the role of metabolic agents like Trimetazidine in patients with angina , low LVEF but there is dearth of literature regarding the role of such therapy on the LV systolic dysfunction in assessment of functional capacity in terms of METS in LV dysfunction and Metabolic syndrome. Metabolic agents which act by partially inhibiting fatty acid oxidation in the cardiac myocyte increase the carbohydrate or glucose which causes a decreased lactic acid production during ischemia. Trimetazidine acts by causing selective inhibition of the fatty acid β-oxidation enzyme 3-keto-acyl-CoA dehydrogenase (3-KAT) with no direct haemodynamic effects.[1] Therefore the mode of action of Trimetazidine is to inhibit the Beta oxidation of free fatty acids (FFAs) and shifting of the metabolism from fatty acid to glucose oxidation which is protective for the ischemic myocardium.[2] Glucose oxidation generates more ATP as compared to the oxidation of equivalent amounts of free fatty acids. There is a convincing evidence based on randomized trials regarding a mortality benefit with Trimetazidine therapy in patients with chronic heart failure and impaired functional capacity.[3]

The purpose of the study was to assess the efficacy of Trimetazidine therapy on functional capacity of patients with left ventricular systolic dysfunction

MATERIAL AND METHODS:

200 patients of all ages and both genders with left ventricular systolic dysfunction were included in the study. This was an open labeled study. Informed consent was taken from all the patients before enrollment and the nature of study along with its duration and drug therapy explained in detail by a doctor in local language during interview. Patients with previous history of CABG or PCI and MI were excluded. Left ventricular systolic function was assessed on Transthoracic echocardiography. Patients with LV dysfunction were divided in to three categories depending upon their LV Ejection Fraction with one group from 35-40% i.e. Moderate systolic dysfunction, second group with LVEF less than 35% and third group with LV EF of 25-30% .i.e. Severe systolic dysfunction. New York Heart Association (NYHA Classification Class I-IV) was used for assessment of the functional status and functional capacity in all cases. A basal Duke Activity Status Index (DASI) score was calculated on a predesigned proforma at the start of the study with a maximum score of 58.2 and METS of 9.8 taken as standard. VO_2 and METS i.e. Metabolic Equivalents were calculated using DASI score. The equation used for METS calculation was: VO_2 Peak (mls/kg) $=0.4\times$DASI SCORE $+9.6$ AND METS$=$ VO_2 Peak/3.5. All these metabolic parameters were recorded. After enrollment and taking basal parameters, all patients received drug therapy with Trimetazidine 70mg in divided doses on daily basis for two months. At the completion of two months treatment all the basal parameters including LVEF, DASI Score, NYHA Class and METS were again calculated in all study cases. The primary end was improvement in functional capacity while secondary end point was improvement in LV systolic dysfunction. The collected data was subjected to statistical analysis using SPSS Version 17.

RESULTS:

Two hundred patients from both genders with age ranging from 20-90 years were enrolled in the study. Mean age of the patients was 49.81 $\pm$10 years. 109 (54.5%) patients were male while 91 (45.5%) patients were female. (Table-I) On completion of the study period statistical analysis of the collected data revealed a significant improvement in all the evaluated parameters including Left Ventricular Systolic dysfunction, VO_2, METS and Functional capacity with sustained release Trimetazidine Therapy of 70 mg daily in divided doses. Significant

improvement in LVEF was observed in the study population. LVEF improved in patients with LVEF of 35% or moderate systolic dysfunction from 120 (60%) patients to a much lower number of 80 (40%) patients at the end of drug therapy with Trimetazidine while cases with LVEF of 25-30% or severe LV systolic dysfunction revealed much better results with improvement from 80 (40%) patients to 16(20%) . An improvement in NYHA Class was also observed like LVEF. Pre Trimetazidine and Post Trimetazidine therapy NYHA Class improvement was seen from 73(36.5% to 41(20.5%) in Class III while Class IV revealed much more improvement from 127 (63.5%) to 73(36.5%). DASI score improved from basal level of 26.30 to a final score of 41.76 with an overall improvement in METS from 5.94 to 7.8 at completion of the study. Table-II

DISCUSSION:

Table-1: Demographic and risk factor profile of the study

N=200		
Age (mean)		49.81 ± 10 Years
Gender	Males	109 (54.5%)
	Females	91(45.5%)
Diabetes Mellitus		144(72%)

Table-II: Pre and post trimetazidine therapy profile of study population at the end of two months

Parameter	Pre Trimetazidine Therapy	Post Treimetazidine Therapy
LVEF	<35% = 120(60%) 25-30% =80(40%)	<35% = 80(40%) 25-30% =16(20%)
NYHA class	Class III= 73(36.5%) Class IV= 127(63.5%)	Class III= 41(20.5%) Class IV= 73 (36.5%)
DASI (mean)	26.30	41.76
METS (mean)	5.94	7.8

The efficacy of Trimetazidine as an antianginal agent in refractory cases is a well-established fact. Besides being a metabolic modulator enhancing the bioenergetics at myocardial cellular level this drug has a definite role in cases with reperfusion injury, nephropathy due to drugs and in peripheral arterial disease along with a promising role in patients with chronic heart failure and disturbed cardiac metabolism due to ischemia.[4] The main stay of drug therapy in patients with chronic angina is relief of symptoms besides improving the quality of life and overall mortality reduction. Contrary to the conventional approach of correcting the oxygen demand and supply mismatch for improving NYHA Class or Angina symptoms is no longer valid on account of the bitter reality that at least one third of our patients with heart failure and angina continue to have persistent symptoms even after a maximized standard drug therapy or even after percutaneous or surgical revascularization. This problem has arisen due to our failure to understand that ischemia is primarily a metabolic disorder. Any drug which shifts the metabolism from free fatty acids to glucose can give excellent results as an adjunctive therapy with other drugs in patients with intractable angina and worsening heart failure despite optimized medical management.[5] Trimetazidine exerts its effects on the myocardial cell as a metabolic modulator without any haemodynamic compromise when used with other antianginal drugs. In one study they reported an improvement in duration of exercise and Functional capacity with NYHA class along with a reduction in number of angina attacks and delayed onset of angina in cases treated with Trimetazidine. This study confirm the results of our research.[6] A reduction in the frequent use of nitrates has also been reported in patients of diabetes mellitus, metabolic syndrome and ischemic heart disease treated with Trimetazidine besides other antianginal drugs. Specific metabolic abnormalities have been implicated in the pathogenesis of cardiomyopathy in diabetic patients. Reduced glucose utilization by the cardiac myocyte due to impaired insulin action in diabetes mellitus results in an increase in free fatty acids leading to an increased utilization of free fatty acids by the myocardium and a reduction in glucose utilization due to which oxygen utilization is increased at mitochondrial level for ATP production. Consequently there is a fall in ATP production impairing myocardial energy production and uncoupling of proteins in mitochondria. Finally myocardial contraction is also impaired. Trimetazidine readjusts and shifts the metabolism from free fatty acid to glucose resulting in normalization of ATP production at cellular level and contractility of the myocyte. This is the main reason for using Trimetazidine in patients with diabetic cardiomyopathy[7].There is convincing evidence of improvement in functional capacity, oxygen consumption, LV ejection fraction, endothelium dependent dilatation and METS in patients on exercise training with regular therapy with Trimetazidine by a study group. They evaluated 116 patients (97 men and 19 women, mean age 58 + 9 years) of Ischemic heart disease and LV dysfunction with ischemic heart disease. They were being followed for cardiac rehabilitation. The results of our study are in strong confirmation of this study.[8] Strenuous exercise can cause damage to the myocardial cells leading to myocardial structural and functional damage resulting from

cardiomyocyte energy metablolic disturbance and oxidative stress. Trimetazidine therapy in such case acts as an anti-ischemic agent which is very effective on account of its anti oxidative and anti-inflammatory effects.[9] Another study evaluated the efficacy of Trimetazidine in combination with exercise on Exercise Capacity and METS along with screening for anti fatal stress ability. They were the first to prove that trimetazidine therapy along with Aerobic Exercise exerts synergistic effects resulting in improvement in METS and exercise capacity. Our study confirms the results of this data evaluation.[10]

Trimetazidine therapy in Heart Failure has resulted in significant improvement in exercise tolerance, functional capacity and NYHA functional class besides improving impaired LV function while many randomised clinical trials have endorsed the usefulness of Trimetazidine as a first line adjunctive therapy in heart failure.[11] A group of investigators evaluated 737 patients with Type II diabetes mellitus and Coronary Artery Disease after administration of Trimetazidine and they concluded that Trimetazidine treatment resulted in improved glucose metabolism, lower HbA1c level and decreased fasting glucose levels with excellent tolerability in all cases under study at the end of six months.[12] We endorse the results of this research group. Trimetazidine addition in the prescription of patients with heart failure without ischemia does not exert beneficial effects on LV systolic function and oxygen consumption.[13]

Efficacy of Trimetazidine is established in treatment of patients with chronic heart failure. It not only reduces major adverse cardiac events but there is documented reduction in overall mortality as well which is associated with long term survival .[14] Trimetazidine is useful and a valid treatment for heart failure patients but its efficacy has not been established in symptomatic patients with non obstructive hypertrophic cardiomyopathy where surgery remains the main stay of treatment.[15] Another group of researchers from Institute of Cardiovascular Diseases in Third Military Medical University evaluated 39 young patients for effect of Trimetazidine therapy on High Altitude Fatigue. They concluded that Trimetazidine has a definite role and efficacy in prevention of High Altitude Fatigue, altitude related cardiorespiratory problems and there is evidence of improved LV systolic function during acute high altitude exposure.[16] Efficacy of preoperative Trimetazidine therapy in patients undergoing Coronary Artery Bypass grafting was evaluated by a group of investigators but no benefit of such a therapy was observed in the study population.[17] Trimetazidine ameliorates symptoms of angina, functional capacity and exercise tolerance in patients with coronary artery disease and heart failure but does not exert any haemodynamic effects. However there is significant reduction in symptoms of angina during exercise with better exercise tolerance in patients with metabolic syndrome and syndrome-X.[18]

CONCLUSION:

Trimetazidine treatment may improve the LV ejection fraction, NYHA Class, Oxygen consumption and functional capacity in symptomatic patients with Left ventricular systolic dysfunction.

REFERENCES

1. William C. Stanley and Mario Marzilli. Metabolic therapy in the treatment of ischaemic heart disease. J Fundamentals and Clinical Pharmacology: the pharmacology of trimetazidine 2003; 02: 133-145.
2. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The anti-anginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ Res. 2000;86:580–588.
3. RomualdoBelardinelli, MaridiaSolenghi, Loretta Volpe et al. Trimetazidine improves endothelial dysfunction in chronic heart failure: an antioxidant effect. European Heart Journal 2007 ; 09:1102–1108.
4. Cian P. McCarthy, Kieran V. Mullins, David M. Kerins. The role of trimetazidine in cardiovascular disease: beyond an anti-anginal agent .:European Heart Journal - Cardiovascular Pharmacotherapy 2016 ;0 4: 266–272.
5. GiacintaGuarini, AldaHuqi,, DoralisaMorrone, Paola Francesca GiuseppinaCapozza, and Mario Marzilli. Trimetazidine and Other Metabolic Modifiers.EurCardiol2018 ; 13(2): 104–111.
6. Csaba A. Dézsi. Trimetazidine in Practice: Review of the Clinical and Experimental Evidence. Am J Ther2016 ; 23(3): e871–e879.
7. Kota SK, , Jammula S, Panda S, Modi KD. Effect of diabetes on alteration of metabolism in cardiac myocytes: therapeutic implications..Diabetes TechnolTher. 2011 ;13(11):1155-60.
8. Belardinelli R, Lacalaprice F, Faccenda E, Volpe L. Trimetazidine potentiates the effects of exercise training in patients with ischemic cardiomyopathy referred for cardiac rehabilitation.. Eur J CardiovascPrevRehabil. 2008 ;15(5):533-40.
9. Zhang H, Liu M1, Zhang Y, Li X. Trimetazidine Attenuates Exhaustive Exercise-Induced Myocardial Injury in Rats via Regulation of the Nrf2/NF-κBSignaling Pathway. Front Pharmacol. 2019 ;10:175.
10. Xie M, Jiang L, Dun Y, Zhang W, Liu S. Trimetazidine combined with exercise improves exercise capacity and anti-fatal stress ability through enhancing mitochondrial quality control..Life Sci. 2019 ;224:157-168.
11. Vitale C, Ilaria S, Rosano GM. Card Fail Rev. .Pharmacological Interventions Effective in Improving Exercise Capacity in Heart Failure. 2018;4(1):25-27.
12. Meiszterics Z, Kónyi A, Hild G, Sárszegi Z, Gaszner B. Effectiveness and safety of anti-ischemic trimetazidine in patients with stable angina pectoris and Type 2 diabetes..J Comp Eff Res. 2017 ;6(8):649-657.
13. Winter JL, Castro PF, Quintana JC et al . Effects of trimetazidine in nonischemic heart failure: a randomized study..J Card Fail. 2014 ;20(3):149-54.
14. Fragasso G, Rosano G, Baek SHet al. Effect of partial fatty acid oxidation inhibition with trimetazidine on mortality and morbidity in heart failure: results from an international multicentre retrospective cohort study. Int J Cardiol. 2013;163(3):320-325.
15. Coats CJ, Pavlou M, Watkinson OT et al .Effect of Trimetazidine Dihydrochloride Therapy on Exercise Capacity in Patients With Nonobstructive Hypertrophic Cardiomyopathy: A Randomized Clinical Trial.. JAMA Cardiol. 2019 ;4(3):230-235.
16. Yang J, Zhang L, Liu C et al .Trimetazidine attenuates high-altitude fatigue and cardiorespiratory fitness impairment: A randomized double-blinded placebo-controlled clinical trial.. Biomed Pharmacother. 2019 ;116:109003.
17. Muhammad Sher-i-Murtaza ,MuhammadZubair ,Anjum Jalal. Is there any benefit of preoperative oral trimetazidine in Coronary Artery Bypass Graft?. J Pak Med Assoc : 2012; 12: 1271-1275.
18. Rogacka, Dorota ;Guzik, Przemyslaw et al. Effects of trimetazidine on clinical symptoms and tolerance of exercise of patients with syndrome X: J Coronary Artery Disease Therapy and Prevention: 2000 ; 2 :171-177.