RESEARCH ARTICLE

To compare the efficacy of trimetazidine and diltiazem in chronic stable angina

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ABSTRACT

Background: Trimetazidine, a cytoprotective agent, is better anti-ischemic drug than conventional agents without causing any change in heart rate and blood pressure. **Aim:** To compare the efficacy of trimetazidine with diltiazem in chronic stable angina. **Materials and Methods:** Thirty diagnosed cases of chronic stable angina were subjected to TMT I with total effort duration and time to precipitate angina being the end point. Patients were given 60 mg of trimetazidine for 8 weeks, in addition to their conventional treatment and subjected to another TMT II with the same end points. After a washout period of 2 weeks, the same patients were put on diltiazem 60 mg TDS for 8 weeks again with another third TMT III to evaluate the results. **Results:** The mean age of all patients was 57.70 ± 8.44. The mean increase in effort duration between TMT II (7.50 ± 1.52) and I (6.21 ± 1.65 min) was 1.29 min which was statistically significant ($P < 0.001$) while difference between TMT III (7.21 ± 1.56) and I (6.21 ± 1.65 min) was 1.0 min ($P < 0.05$ s). The difference observed between TMT III and II was 0.29 ($P > 0.05$ not significant). The increase in time to ST-segment depression between TMT I and II was 1.35 min. ($P < 0.001$), whereas the difference between TMT I and III was 1.01 min ($P < 0.05$ significant). Anginal attacks per week with diltiazem were 1.81 ± 0.59 and 1.67 ± 0.52 with trimetazidine ($P > 0.005$). **Conclusions:** The patients with stable angina had a better clinical improvement after treatment with trimetazidine, without any adverse effects.

KEY WORDS: Stable Angina; Diltiazem; Trimetazidine; Metabolic Modulators; Cytoprotection

INTRODUCTION

Evidence-based pharmacologic interventions for ischemic heart disease (IHD) are aimed to reduce the risk of future events and improving the quality of life. Conventional pharmacological treatment in the form beta-blockers, calcium channel blockers (CCBs), and long-acting nitrates improve ischemia by affecting hemodynamic system.[1]

The antianginal effects of CCBs like diltiazem have been well established. The beneficial role of diltiazem in the case of IHD is probably due its vasodilating effect over coronary vasculature and cardiac conductive tissues (negative chronotropic effect and prolongation of atrioventricular [AV] conduction). This same effect over cardiovascular system, on the other hand, may cause problems like sinus bradycardia and occasionally AV block.[2]

However, many patients remain uncontrolled due to side effects or refractory symptoms. In those patients, newer

antianginal medications can be added, without causing any deleterious hemodynamic compromise as these agents have different mechanisms of action from the traditional agents.[3,4] These drugs increase glucose metabolism at the expense of free-fatty-acid metabolism, enhancing oxygen efficiency during myocardial ischemia. Trimetazidine acts as anti-ischemic agent by metabolic modulation. Trimetazidine shifts metabolism from FFAs (β-oxidation) to glucose (glycolysis) without affecting blood pressure (BP) or myocardial contractility.[4,5] The main side effects are gastric discomfort, nausea, headache, and movement disorders.[6] In France, Levy had done randomization of stable angina patients and administered trimetazidine (60 mg/24 h) to diltiazem (180 mg/24 h). The comparison of exercise test was performed at inclusion and after 6 months of therapy and showed that the exercise time was significantly prolonged ($P < 0.05$).[7]

Hence, this study was planned to evaluate the efficacy of trimetazidine with diltiazem in chronic stable patients.

MATERIALS AND METHODS

Thirty diagnosed cases of chronic stable angina, on conventional treatment, attending cardiology, and medicine outpatient department of Maharishi Markandeshwar Medical College and Hospital, Solan, were taken up to study. The basic clinical status of the patient was assessed by biochemical parameters such as fetal bovine serum, serum creatinine, serum cholesterol, and triglycerides. These patients were subjected to TMT I with total effort duration and time to angina being the end point. After that, patients were given 60 mg of trimetazidine in three divided doses of 20 mg each for a period of 8 weeks, in addition to their conventional treatment which they were already taking. At the end of 8 weeks, patients were subjected to another TMT II with same end points. After a washout period of 2 weeks during which no treatment was given except the conventional treatment, the same patients were put on diltiazem 60 mg TDS for 8 weeks again in addition to their conventional treatment which they were already taking. At the end of 8 weeks, patients were subjected to another TMT III with same end points.

Methodology of Stress Test

Patients were instructed to come to the TMT room in the morning. They were also instructed not to drink caffeinated beverages or smoke or eat three hours before testing and wear comfortable shoes and loose-fitting clothes. Adequate skin preparations were done so that good signal to noise ratio was obtained. The testing room war air-conditioned and temperature was kept comfortable. The skin test was conducted on MORTARA X-SCRIBE, a computerized stress testing system in Cardiology Department of Medical College.

A preliminary 12 lead electrocardiogram (ECG) was done on all patients. The electrodes were applied to the torso to reduce motion artifacts as per the Mason-Liker modification of the 12 lead ECG. TMT was done according to the Bruce protocol. The gradient of exercise machine and walking speed was increased in 3 min stages:

Stages	Speed (KMPH)	Elevation (% grade)	Duration (min)
1	2.6	10.0	3
2	3.8	12.0	3
3	5.4	14.0	3
4	6.8	16.0	3
5	8.0	18.0	3
6	9.0	20.0	3

The data of patients - such as name, age, sex, weight, and BP - were recorded in the computer. Treadmill walking was demonstrated to the patients and the testing was started.

BP was recorded at the end of every stage and entered in data. Exercise testing was considered negative if the patient had exercised adequately for his age and no significant changes were found. A positive test was defined as at least 1 mm flat or down-slopping ST-segment depression measured at 80 ms after the J point. The presence or absence of angina was also noted. The test was stopped in between if the patient developed any of the following indication:
1. Severe fatigue or dyspnea
2. Ataxia
3. Grade ¾ chest pain
4. Ischemic ST-segment elevation more than 3.0 mm
5. Ischemic ST-segment elevation more than 1 mm in a non-Q wave lead
6. Unsuspected appearance of ventricular tachycardia
7. Ectopic supraventricular tachycardia
8. Progressive reproducible decrease in systolic BP
9. Abnormal elevation of systolic BP
10. Decreasing heart rate
11. Technical problems interfering with ECG or BP interpretation.

The data of exercise testing in each patient was recorded on the thermal paper and analyzed and compared at the end of 3rd TMT of following parameters:
1. Total duration of exercise
2. Maximum ST-segment depression
3. Time to 1 mm ST-segment depression
4. Presence or absence of angina.

Patients in congestive cardiac failure, unstable angina, bronchial asthma, peripheral vascular disease, Post-angioplasty patients, and post-coronary artery bypass patients were excluded:

Patients were asked to record the number of times they had angina during the periods trimetazidine and diltiazem were given and also number of times they had to take sublingual nitrates during the duration of each drug.

The following parameters were assessed:
1. Comparative improvement in TMT findings with diltiazem therapy and with trimetazidine
2. Clinical improvements:
    a. The frequency of angina attack in a period of each drug was given,
    b. The frequency at which sublingual nitrates had to be taken in the period each drug was given for relief of angina.

RESULTS

Figure 1 showed that the age distribution of the people who participated in the study. Most of the patients were of age group 51-60 years (43.33%). The youngest patient was of 42 years while the oldest as 72 years. The mean age of all patients was 57.70 ± 8.44.
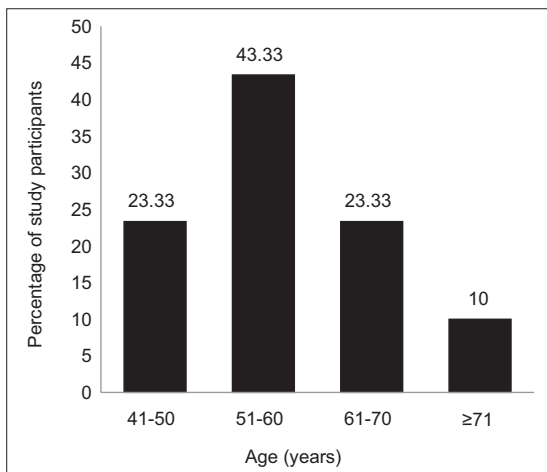

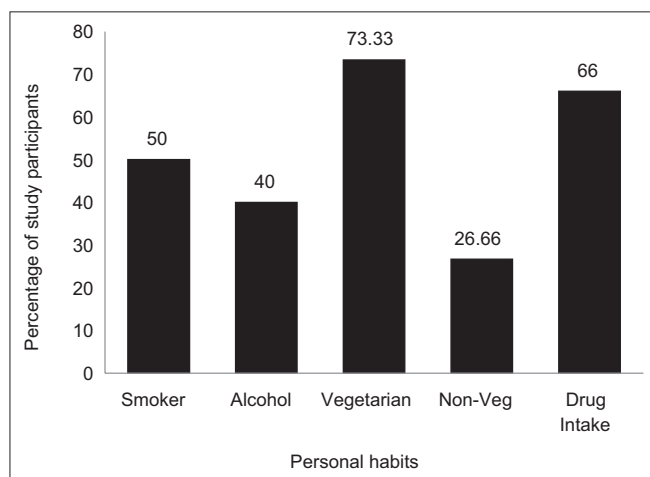**Figure 1:** Age distribution of study group

Figure 2: Personal habits of the patients

Figure 2 showed that a total of 50% (65.2% of males) were smokers (some overlapping between different habits). Twelve males (52.17%) were alcoholic with the majority of them being mild to moderate drinkers. Vegetarians were 22 (73.33%), whereas non-vegetarians were 8 (26.66%).

The mean in exercise time after TMT I (0 week) which was 6.21 ± 1.65 min, while after TMT II (at 8 weeks of trimetazidine) the exercise time increased to 7.50 ± 1.52 and the time after TMT III (at 8 weeks of diltiazem) was 7.21 ± 1.56. The difference ion maximum exercises time (in min) between TMT II and I was 1.29 min which was statistically significant ($P < 0.001$), while difference between TMT III and I was 1.0 min which was statistically significant ($P < 0.05$). The difference observed between TMT III and II was 0.29 which was not statistically significant as shown in Table 1 ($P > 0.05$).

In TMT I (baseline), the maximum mean ST-segment depression was 2.71 ± 0.66 (mm). In TMT II (trimetazidine), the mean was 2.08 ± 0.62, whereas in TMT III was 2.37 ± 0.65. The decrease in maximum ST-segment depression with trimetazidine was 0.63 as compared to baseline. With diltiazem was 0.34 as compared to baseline ($P < 0.05$ significant). Mean increase in ST-segment depression was 0.29 with trimetazidine was comparable. When maximum ST-segment depression with trimetazidine was compared with that of diltiazem, it was found trimetazidine decreased the ST-segment depression by 0.29 mm as compared with diltiazem as shown in Table 2 (P value not significant).

The mean time taken to 1 mm ST-segment depression TMT I was 3.44 ± 1.76 (in min) in TMT II the mean time was 4.59 ± 2.18, whereas in TMT III the mean time was 4.45 ± 2.06 (in min).

Table 1: Comparison of exercise time (in min) between the TMT'S

Comparison	Increase in ET (in minute)	SE	*t*	*P*
TMT II versus I	1.29	0.40	4.25	<0.001
TMT III versus I	1.0	0.41	2.41	<0.05
TMT II versus III	0.29	0.38	1.83	>0.05

SE: Standard error

Table 2: Comparison of maximum ST-segment depression in TMT I, II and III

Comparison	Decrease	SE	*t*	*P*
TMT II versus I	0.63	0.16	3.93	<0.01 HS
TMT III versus I	0.34	0.16	2.112	<0.05 S
TMT II versus III	0.29	0.16	1.81	>0.05 NS

SE: Standard error, NS: Not significant, S: Significant, HS: High significant

It is observed that the increase in time to ST-segment depression between TMT I and II was 1.35 min which was statistically highly significant ($P < 0.01$). The difference between TMT I and III was 1.01 min, it was statistically significant ($P < 0.05$). However, the difference between TMT II and III was 0.14 min which was not significant statistically as shown in Table 3 ($P > 0.05$).

Table 4 shows the clinical parameters. Anginal attacks per week 1.81 ± 0.59 when on diltiazem and 1.67 ± 0.52 when on trimetazidine. The difference was 0.14. Attacks per week which was not statistically significant ($P > 0.005$). Only 9 patients had to take sublingual nitroglycerine for relief of angina attacks. The average number of sublingual nitroglycerine was 0.28 while on diltiazem and 0.34 while on trimetazidine. The difference was 0.06 and was not statistically significant ($P > 0.05$).

DISCUSSIONS

This study was a cross-over trial designed to test the comparative efficacy of trimetazidine and diltiazem in patients with chronic stable angina. The clinical and exercise test results were assessed.

Exercise time was significantly increased while the patients were put on trimetazidine as well as diltiazem. This value is concordance with other studies. In a study conducted by Sellier et al. showed similar results. The acute effect of single dose of 60 mg trimetazidine was evaluated in a double-blind placebo controlled crossover study. In this study, the exercise time from 7.7 ± 0.4 min with placebo to 9.0 ± 0.5 min with trimetazidine.[8] Dalla-Volta et al. found that trimetazidine increased the exercise capacity and showed significant improvement in total work performed.[9] Michaelides et al. compared the therapeutic benefits of trimetazidine with that of isosorbide dinitrate in the 53 patients with stable angina

uncontrolled by propranolol 40 mg BID. They concluded that as far as the stress test is concerned analysis of variance showed a significant more pronounced improvement in the trimetazidine group than the isosorbide nitrate group with respect to exercise time.[10]

De Backer and Vincke et al., studied the effect of diltiazem in a double-blind placebo-controlled study of 8 weeks. Diltiazem was effective in increasing the angina threshold, in decreasing the ST-segment depression at an identical submaximal workload and in increasing its time to termination of exercise.[11]

Maximum ST-segment depression was 0.63 mm with trimetazidine and 0.65 with diltiazem which was statistically significant ($P < 0.05$). In a trial conducted by Michaelides et al. the maximum ST-segment depression was reduced from 2.75 ± 0.16 to 2.58 ± 0.17 when trimetazidine was added to the treatment regimen.[10] Nalbantgil et al. showed that the maximum ST-segment depression was less in patients with trimetazidine than those of placebo.[12]

In a study conducted by Desideri and Celegon, trimetazidine significantly increased time to 1 mm ST-segment depression. Similar results were observed by Sellier and Dalla-Volta et al.[9,13,14]

In France, Levy had studied the effect of trimetazidine (60 mg/24 h) to diltiazem (180 mg/24 h) in the stable exertional angina insufficiently improved by CCB alone. Comparison of the stress tests performed at the 6th month showed that the ischemic threshold of 1 mm was significantly delayed by 2 min 41 s in the trimetazidine group ($P < 0.001$) versus 42 s in the placebo group (NS). The exercise time was also significantly prolonged ($P < 0.05$).[7]

In another study done by Manchanda and Krishanswami in 1997 concluded that patients with stable angina uncontrolled with diltiazem had a clinically important improvement after combination treatment with trimetazidine, without adverse hemodynamic events or increased side effects. As compared to placebo, there was net improvement with trimetazidine in mean anginal attacks of 4.8/week, in mean exercise times at 1 mm ST-segment depression of 94.2 s and at onset of angina of 113.1 ($P < 0.05$).[15]

CONCLUSIONS

Both the drugs are comparable antianginals as they produce almost similar increase in increase time and time to 1 mm ST-segment depression and symptomatic improvement in chronic stable angina patients. However, they have different mechanisms of action. They may thus be used together or trimetazidine can be used alone in situations where there are contraindications to the use of diltiazem.

Table 3: Comparison of time to 1 mm (in min) ST-segment depression between the TMT'S

Comparison	Increase (in minute)	SE	*t*	*P*
TMT II versus I	1.15	0.50	2.70	<0.01 HS
TMT III versus I	1.01	0.48	2.10	<0.05 S
TMT II versus III	0.14	0.54	0.62	>0.05 NS

SE: Standard error, NS: Not significant, S: Significant, HS: High significant

Table 4: Clinical parameters after drug therapy

Drugs	Anginal attacks per week	Sublingual nitroglycerine
Diltiazem	1.81±0.59	0.28
Trimetazidine	1.67±0.52	0.34

REFERENCES

1. Pauly DF, Pepine CJ. Ischemic heart disease: Metabolic approaches to management. Clin Cardiol. 2004;27(8):439-41.
2. Klinke WP, Kvill L, Dempsey EE, Grace M. A randomized double-blind comparison of diltiazem and nifedipine in stable angina. J Am Coll Cardiol. 1988;12(6):1562-7.
3. Lee L, Horowitz J, Frenneaux M. Metabolic manipulation in ischaemic heart disease, a novel approach to treatment. Eur Heart J. 2004;25(8):634-41.
4. Pornin M, Harpey C, Allal J, Sellier P, Ourbak P. Lack of effects of trimetazidine on systemic hemodynamics in patients with coronary artery disease: A placebo-controlled study. Clin Trials Metaanal. 1994;29(1):49-56.
5. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal 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(5):580-8.
6. Martí Massó JF, Martí I, Carrera N, Poza JJ, López de Munain A. Trimetazidine induces parkinsonism, gait disorders and tremor. Therapie. 2005;60(4):419-22.
7. Lévy S. Value of the combination of trimetazidine (vastarel 20 mg) with diltiazem (tildiem 60 mg) in stable effort angina. A double-blind versus placebo multicenter study. Ann Cardiol Angeiol (Paris). 1995;44(4):203-12.
8. Sellier P, Audouin P, Payen B, Corona P, Duong TC, Ourbak P. Acute effects of trimetazidine evaluated by exercise testing. Eur J Clin Pharmacol. 1987;33(2):205-7.
9. Dalla-Volta S, Maraglino G, Della-Valentina P, Viena P, Desideri A. Comparison of trimetazidine with nifedipine in effort angina: A double-blind, crossover study. Cardiovasc Drugs Ther. 1990;4 Suppl 4:853-9.
10. Michaelides AP, Spiropoulos K, Dimopoulos K, Athanasiades D, Toutouzas P. Antianginal efficacy of the combination of trimetazidine-propranolol compared with isosorbide dinitrate-propranolol in patients with stable angina. Clin Drug Investig. 1997;13(1):8-14.
11. De Backer G, Vincke J. Double-blind comparison of Diltiazem and placebo in the treatment of exercise-inducible chronic stable angina pectoris. Acta Cardiol. 1982;37(4):245-55.
12. Nalbantgil S, Altintig A, Yilmaz H, Nalbantgil II, Önder R. The effect of trimetazidine in the treatment of microvascular angina. Int J Angiol. 1999;8:40-43.
13. Desideri A, Celegon L. Metabolic management of ischemic heart disease: Clinical data with trimetazidine. Am J Cardiol. 1998;82(5A):50K-3.
14. Sellier P. The effects of trimetazidine on ergometric parameters in exercise-induced angina. Controlled multicenter double blind versus placebo study. Arch Mal Coeur Vaiss. 1986;79(9):1331-6.
15. Manchanda SC, Krishnaswami S. Combination treatment with trimetazidine and diltiazem in stable angina pectoris. Heart. 1997;78(4):353-7.