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Research Article

ROLE OF TRIMETAZIDINE, A CYTOPROTECTIVE AGENT IN ISCHEMIC HEART DISEASE

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ABSTRACT

Objectives: Metabolic agents such as trimetazidine offer a benefits role of cytoprotection in ischemic heart disease (IHD) through an inhibition of cardiac fatty acid oxidation and improving myocardial glucose utilization. To show the efficacy of trimetazidine in reducing the incidence of angina and improving exercise tolerance.

Methods: 50 diagnosed cases of chronic stable angina taking conventional treatment were subjected to stress test (treadmill) on day 0 to evaluate the parameters such as effort duration and ST-segment changes at the end of the exercise. After evaluation, the patients will be given trimetazidine for a period of 6-week at a dosage of 60 mg (in three divided doses) daily. After completion of the stipulated period, a second stress test evaluation was done.

Results: The present study consisted of 50 patients of chronic stable angina, out of which 35 were males and 15 were female patients. It was seen that trimetazidine intake brought about an increase in the mean exercise time from 7.086±0.96 to 8.3±0.75 and showed good symptomatic improvement (in 31 patients). 15 patients did not show any appreciable (>1 minute) increase in the effort duration. No severe symptoms were reported to warrant discontinuation of the drug.

Conclusion: Trimetazidine is an effective anti-anginal as monotherapy as well as an adjuvant to conventional anti-anginals as a cytoprotective agent.

Keywords: Trimetazidine, Cytoprotective, Metabolic modulator, Ischemic heart disease.

INTRODUCTION

India is showing a health transition phase of rising proportions of the epidemic for coronary heart disease [1]. India has reported a high burden in the levels of conventional risk factors such as diabetes, hypertension, and metabolic syndrome leading to ischemic heart disease (IHD) [2-4]. There occur reduced oxygen consumption and adenosine triphosphate (ATP) formation in the mitochondria and accelerated anaerobic glycolysis, lactate accumulation, and cell acidosis in myocardial ischemia [5].

IHD has long been considered in terms of hemodynamics to render the patient asymptomatic by conventional treatments such as nitrates, beta-blockers, and calcium channel blockers or potassium channel openers. These drugs either decrease cardiac work or increase blood supply. However, all were unable to meet the end points of IHD. In the beginning of 1990, a new research has been directed toward myocardial cytoprotection through metabolic modulation which showed that nearly half the IHD patients rendered asymptomatic [6].

Trimetazidine, a cytoprotective agent, acts at the cellular level to cause a shift between fatty acid oxidation and carbohydrate oxidation. It delays the switch off of mitochondria in the respiratory chain and delays the onset of anaerobic glycolysis. As a result, it prevents free radical generation, maintains ATP production, and reduces intracellular acidosis. Its potent activity prevents membrane damage and cell death by decreasing sodium and calcium concentration [7,8].

Trimetazidine has been found to have an inhibitory effect on thrombin-induced aggregation by decreasing the calcium influx evoked by thrombin. So, this antiplatelet activity also reduces the occurrence of acute events such as myocardial infarction [9].

Trimetazidine is a potentially lifesaving drug that acts via a unique mechanism of action, altering heart cell metabolism to utilize glucose instead of fat. So, this study was done to improve the exercise tolerance in IHD.

METHODS

50 diagnosed cases of chronic stable angina, on conventional treatment, attending Maharishi Markandeshwar Medical College and Hospital, Solan (Indoor and Outdoor) were enrolled in the present study. All patients irrespective of their age, gender, or the presence of other primary pathology were taken up for study. On the day of doing a test just before the test, written consent of the patient to undergo submaximal graded exercise testing was obtained in all the patients.

In each selected patients, a detailed history was recorded and during their stay in the hospital development of any complication was noted. Findings of general physical examination and cardiovascular examination done at the time of admission were recorded. Detailed general physical examination and cardiovascular examination was done immediately before doing a stress test. The basic clinical status of the patients was assessed by biochemical parameters such as fasting blood sugar (FBS), serum creatinine, serum cholesterol, and triglycerides.

After proper selection of patients, all of them will be subjected (irrespective of what other conventional anti-anginal drugs that they are taking) to stress test (treadmill) on day 0. The parameters of exercise tests are noted. After evaluation, the patients will be given trimetazidine for a period of 6-week at a dosage of 60 mg (in three divided doses) daily. After completion of the stipulated period, the patient was subjected to another stress test and the parameters evaluated on day 0 are again recorded.

Resting electrocardiographs (ECG) were recorded in supine and standing postures. ECG was also recorded after hyperventilation. To obtain effective hyperventilation, the patient was asked to breathe in and out until he/she felt dysphonic and the heart rate went up by at least 10 beats/minute as compared to resting heart rate. The ECG thus obtained was compared with previous one and any new abnormality was noted down.

Treadmill was set according to Bruce protocol. Cardiac monitor was connected to ECG machine and lead V5 was recorded before starting exercise. Cuff of dial type sphygmomanometer was wrapped around the right upper arm and blood pressure recorded immediately before starting exercise and during the middle of each stage.

During the first stage, the speed of the machine was adjusted at 2.6 KMPH and an elevation of 10% and the time was set for 3 minutes. During the middle of each stage, blood pressure was recorded. After every 3 minutes, the next stage was started and speed and elevation adjusted according to the stage. Before starting next stage, the patient was asked for the development of any symptoms and if he/she was able to do more exercise. Continuous monitoring was done during exercise and in the post-exercise period up to 10 minutes.

The exercise was terminated when any of the following sign and symptoms appear such as fatigue or dyspnea, chest pain, dizziness, claudication, blood pressure rises more than 200/120 mm of Hg and inability of BP and heart rate to rise with exercise. It was also terminated if ECG changes showed ST-segment depression (horizontal or downsloping) of more than 0.3 mV or 0.2 mV or appearance of multifocal premature ventricular beats or any arrhythmia. Immediately, before and after the termination of exercise V5 was recorded.

Recording of 12 lead ECG and blood pressure was also done in the post-exercise period at 1, 3, 6, and 9 minutes. The patient was regularly asked about the development of chest pain or other symptoms in the post-exercise period up to 10 minutes. After the stress test, the patient was observed during and for 1 hr for the development of any symptoms or complications.

Interpretation of stress test was done by grading system given by Selzer *et al*., in 1978, as normal ECG responses (negative test), uninterpretable exercise test response, mildly positive ECG responses (+), moderately positive ECG responses (++), and strongly positive ECG responses (+++) [10].

RESULTS

Table 1 showed the age and sex distribution of the people who participated in the study. Most of the patients were of the age group of 51-60 years. The youngest patient was a 39-year-old man, and oldest was a 68-year-old male.

35 patients were males, and 15 patients were females. 46% of all the males who participated were in the age group of 51-60, and 60% of all the females were in the age group of 51-60. The majority of the patients were light to moderate workers with 46% being sedentary workers, 38% were moderate workers, and only 16% were heavy workers.

The Graph 1 shows that a total of 32% (45.7% of males) were smokers. None of the females were smokers. 27 males (54%) were alcoholic with the majority were mild to moderate drinkers. Only 7 persons consumed 3-4 ounces/day. Non-vegetarians constituted 34% of the total and took meat approximately twice a week.

Out of the 50 patients, as many as 35 (70%) had evidence of hypercholesterolemia, 18 patients (36%) were hypertensive, and 13 were diabetic. Out of the 35 males, 16 (46%) were smokers (approximately>cigarettes or bidis/day) as shown in Graph 2.

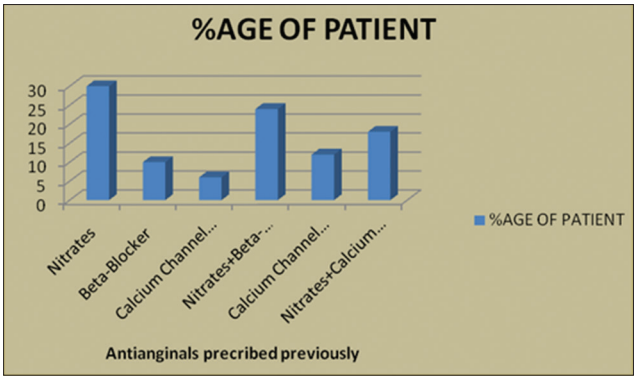
A maximum number of patients (44%) had both pain and breathlessness as the initial presenting complaint with 15 patients (30%) had only pain and out of those 4 patients had a complaint of atypical pain.

17 patients (34%) showed FBS values above 100 mg% while 35 (70%) patients showed serum cholesterol <200 mg%. Furthermore, 34 (68%) of the patients showed increased triglyceride levels. Only 6 people had serum creatinine levels > 2 mg%

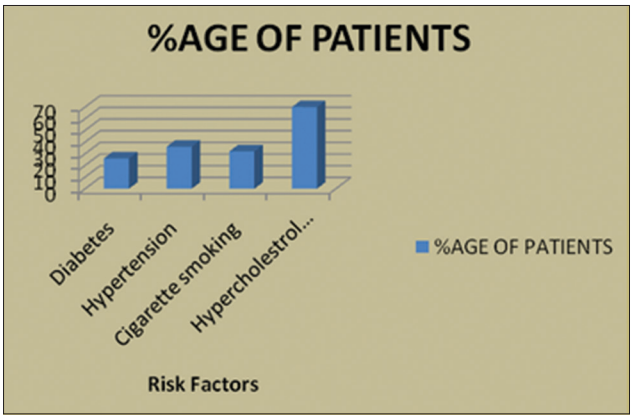
The Graph 3 shows the various anti-anginal drugs that the patients were taking before the start of the study with 23 patients (46%) were

Table 1: Age and sex distribution among study population

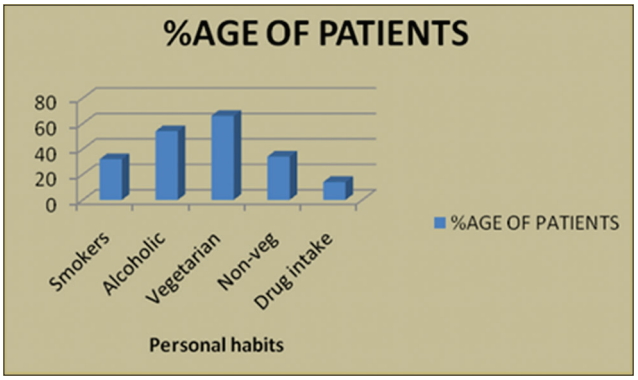
Age group	Male	Female	Percentage of patient
<40	2	-	4
41-50	11	1	24
51-60	16	9	50
61-70	6	5	22
>70	-	-	-



Graph 1: Personal habits in study group



Graph 2: Prevalence of risk factors of ischemic heart disease



Graph 3: Number of patients on various anti-anginal drugs (before trimetazidine)

Table 2: Symptomatic improvement in patients after trimetazidine

No. of patients showing improvement	Pain (normal exertion)	Pain and dyspnea	Dyspnea	Weakness	Palpitation and dyspnea
Presenting compliant before therapy	15	22	10	1	2
No. of patients showing improvement after trimetazidine therapy	10	12	6	1	2

on a single drug and 9 patients (18%) were on a maximum of three drugs. 18 patients (36%) were on a combination of 2 drugs.

The 50 patients who were subjected to the stress test on day 0 had exercise time ranging from 3 to 10.5 minutes. The mean exercise time lies between 7.086±0.96 (6.126 minutes-8.046 minutes).

After drug treatment (trimetazidine) for 6 weeks, patients were again subjected to a TMT. The exercise time ranges from 4 minutes to 12 minutes

Out of 50 patients receiving trimetazidine, 31 patients showed clear cut symptomatic improvement. There was a decrease by 54.5% in the patient complaints of both pain and breathlessness as shown in Table 2.

Table 3 showed that out of a total of 50 patients 16 (32%) had improvement < 1 mm while 34 (68%) had more than 1 minute improvement in total exercise time.

34 (68%) of the patient showed improvement in the ECG changes taken at the end of exercise time. Out of 9 patients on multiple anti-anginal drugs only 2 patients showed improvement. It was seen that trimetazidine intake brought about an increase in the mean exercise time from 7.086±0.96 to 8.3±0.75 and showed good symptomatic improvement (in 31 patients) ($p<0.05$ significant).

Out of the 50 patients studied only 6 patients reported side effects referable to the gastrointestinal system in the form of pain in the epigastrium. No severe side effects were detected to warrant the discontinuation of the therapy.

Table 3: ST-segment improvement and increase in exercise time (after trimetazidine)

Sign and Symptom improvement	Increase in exercise time		Improvement in ST-segment
	<1 minute	>1 minute	
No. of patients	16	34	33
Percentage of patients	32	68	66

DISCUSSION

The present study deals with the clinical evaluation of a cytoprotective anti-anginal trimetazidine in chronic stable angina patients. In this study, 6 weeks' treatment with trimetazidine significantly improved treadmill exercise test parameters and significantly reduced clinical symptoms.

Data from the previous studies revealed the same results as this study. In a trail of trimetazidine as a monotherapy, Detry *et al*., 1994 compared its effect with a placebo and concluded that trimetazidine reduces the incidence of angina and improves exercise tolerance [11].

In another important double-blind, placebo-controlled study, Sellier and Broustet evaluated the efficacy of trimetazidine modified release 70 mg/day in a group of 223 patients with angina pectoris who were insufficiently controlled with 50 mg/day of Atenolol after 2 months of therapy. After 8 weeks, the authors observed a significant increase in the time to 1 mm ST-segment depression in exercise tests (+34.4 s, p=0.03) in the trimetazidine group in comparison with the placebo group [12].

In a mata analysis done by Marzilli and Klein (2003) of 12 trials including 868 patients, trimetazidine was found to significantly increase exercise duration to 1 mm ST-segment depression on the exercise test, and to reduce weekly episodes of angina, both as monotherapy and as add-on therapy [13]. In the largest meta-analysis conducted on the effects of trimetazidine instable angina pectoris patients, Danchin *et al*. evaluated 218 trials with a total 19,028 patients, including the results of the VASCO trial. Trimetazidine significantly improved exercise tolerance, weekly angina episodes, and use of short-acting nitrates when compared with placebo [14]. The drug had no effect on BP and heart rate. The lack of effects on heart rate and blood pressure offers a potential advantage in conditions of bradycardia and arterial hypotension.

In the present study, trimetazidine was used as an adjuvant therapy with other anti-anginal agents where it showed its additives effect to other anti-angina agents.

TRIMPOL-I study, TRIMPOL-II study, and VASCO study were the studies providing evidence generated in support of trimetazidine as an add-on to beta-blockers in symptomatic patients with angina pectoris [14-16]. Two other studies by Manchanda and Krishnaswami supported the efficacy of Trimetazidine as an additional therapy to calcium channel blockers [17,18].

By reviewing the past and present trials, it is evident that trimetazidine is an effective anti-anginal which can be used as monotherapy or in combination with other anti-anginals. It can be effectively combined with other anti-anginal drugs such as nitrates, β-blockers, and calcium channel blockers.

The incidence of adverse effect in this study was few (6 patients) and was of a mild nature in the form of gastrointestinal side effects.

CONCLUSION

Trimetazidine is an effective anti-anginal at a dose of 60 mg daily (in three divided doses). It is effective as monotherapy as well as in combination. Its novel cytoprotective action in contrast to hemodynamic altering anti-anginal agents makes it an effective adjuvant to conventional anti-anginals.

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