EFFICACY OF TRIMETAZIDINE IN CHRONIC STABLE ANGINA PATIENTS RECEIVING MAXIMALLY-TOLERATED BACKGROUND MEDICAL THERAPY

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Author's Contribution

SA:Conducted the study and wrote the article. CMUR: Helped in review the article. ME: Re-arranged data and corrected article. ZM: Tables and figures. SN and FM made corrections and did the proof reading.

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ABSTRACT

BACKGROUND: There are many presentations of coronary artery disease. Out of which chronic stable angina is one variety. This study was designed to see the effectiveness of trimetazidine as an anti angina option.

OBJECTIVE: To compare the frequency of angina attacks per week in patients using Trimetazidine vs Placebo.

MATERIAL & METHODS: This Randomized controlled trial was carried out in Out Patient Department, Punjab Institute of Cardiology, Lahore from 04-09-2017 to 04-03-2018 after approval from ethical committee. After written and informed consent 256 patients fulfilled selection criteria were enrolled and two equal groups were made. Group one was treated with Trimetazidine and control was treated with their previous medicine and placebo and assessed for number of anginal attacks per week. The collected data was analysed by SPSS.

RESULTS:The mean age of patients was 49.5 ± 6.8 years. There were 150 (58.5%) males and 106 (41.5%) females. The mean attack of angina in TMZ group reduced from 5.06 ± 2.03 (p value 0.15) to 3.6 ± 2.2 (p value 0.000) in TMZ group as compared to placebo group i.e 5.5 ± 3 to 5.4 ± 2.6 and it was more effective with shorter duration of disease.

CONCLUSION: It has been concluded that the frequency of angina attack reduced in patients using trimetazidine.

KEY WORDS: Angina, Placebo, Trimetazidine, shorter duration

INTRODUCTION:

Cardiovascular diseases (CVDs) has become the main cause of mortality around the globe. The mortality due to CVDs was 17.5 million in 2012 i.e. 3 deaths out of every 10 patients. Of these, 7.4 million suffered death due to Coronary Artery Disease. About three quarters of these deaths occurred in poor socioeconomic countries like Pakistan and India.[1] In 2012 the population of Pakistan was above 180 Millions. About 1.3 million deaths occurred in that year of which 19% were due to CVDs.[2]

There are many presentations of coronary artery disease. Out of which chronic stable angina is one variety. Chronic stable angina, is defined as chest discomfort or pain of less than 10 minutes duration, precipitated by stress or exertion which may get better by nitroglycerine or rest, is a major presenting complaint in such patients. The risk of acute coronary syndrome doubles if the patient has chronic stable angina.[3] Lifestyle modification with antianginal medications including beta-blockers, calcium-channel blockers, nitrates and recently ranolazine and trimetazidine and revascularization etc. are treatment modalities for angina.

Trimetazidine, a metabolic modulator is a partial inhibitor of long-chain 3-ketoacyl thiolase (3-KAT) which leads to shift of cardiac myocte metabolism to a lower oxygen consumption level during oxidation of glucose. It is not a first line treatment in the management of chronic angina but may be used for refractory angina despite beta blocker and nitrates. It has no effect on blood pressure or heart rate.

Previous studies have shown favourable outcome of adding trimetazidine in refractory angina. In a double blind study including 426 patients of chronic angina,(TRIMPOL-II), trimetazidine showed noticeable improvement in exercise capacity evidenced by exercise parameters compared to placebo: total increase in exercise duration of +65s for Trimetazidine group vs +26s for Placebo group, p=0.023, time to 1-mm ST-segment depression of 86s for Trimetazidine group vs +26s for Placebo group, p=0.003, angina attacks/week of -1.9 for Trimetazidine group vs -0.9 for Placebo group, p=0.014 and short acting nitrates consumption/week of -1.3 for Trimetazidine group vs -0.5 for Placebo group, p=0.032, without hemodynamic changes.[4] Another study including 223 patients also showed similar outcomes (Sellier),i.e. trimetazidine produced a significant increase in the time to 1-mm ST-segment depression of +64s in Trimetazidine group vs +24s in Placebo group in exercise tests.[5]

The purpose of this study was to analyze antianginal effectiveness of trimetazidine as no local data is available regarding the efficacy of this novel drug as it has shown benefits in stable angina patients in clinical trials in international studies. This study will not only help patients who are taking maximum conventional drug treatment and experiencing less control of symptoms but also it will delineate guidelines for management of such patients. It will improve quality of life and there will be less need for revascularization or bypass surgery for which expertise and specialized centers are already rare. Many patients die due to lack of these specialized facilities.

MATERIAL AND METHODS:

This Randomized controlled trial was conducted in Out Patient Department, Punjab Institute of Cardiology, Lahore from 04-09-2017 to 04-03-2018 after approval from ethical committee.

SAMPLE SELECTION:

Using 95% confidence level, 80% power of study, a sample of 256 cases was determined, ratio of sample B:A of 1 Mean value 3.3 ±4.2 in group A (Trimetazidine) Mean value 2.15±2.4 in group B (Control) 128 in each group. Consecutive non-probability sampling technique was used. Patients having age 18-60 years having Chronic Stable Angina who were already taking maximally tolerated background anti anginal therapy for at least 3 months regardless of gender were included while Pregnant and lactating mothers, Patients with Parkinsons Disease, Renal Failure (creatinine clearance < 30ml/min) were excluded. More over Patients taking CYP3A inducers (e.g., rifampin, Phenobarbital) and CYP3A inhibitors (e.g., ketoconazole, clarithromycin) were also excluded.

OPERATIONAL DEFINITION:

Chronic Stable Angina Patients with typical features of angina of at least 3 months duration characterized by central/ left sided chest pain precipitated by exertion which is relieved by taking rest or sublingual nitroglycerin.

Angina Retrosternal chest pain which may radiate to the jaw, neck and arms, which is related with exertion and relieved at rest.

Maximally tolerated background therapy. Therapy consisting of Beta Blocker (e.g. Metoprolol 25-100mg/day etc), Calcium Channel Blocker (e.g. Diltiazem or Amlodipine 5 to 10mg/day etc) and Nitrate (e.g. Glyceryl Trinitrate 6.4-19.2mg/day) at maximally tolerated doses where haemo-

dynamic status is not affected i.e. blood pressure (90-120/60-80mmHg) and pulse(60-80/min) remain in desired ranges.

DATA COLLECTION PROCEDURE:

After approval from Ethical Review Board 256-patients presenting in PIC OPD were enrolled with consent. Patients were randomly divided (flipping a coin) in two groups A and B each. Information regarding their demographic data was noted in the Performa. History and physical examination was done along with the review of previous record. At the start of study number of angina attacks per week was noted. Group A was prescribed trimetazidine 35mg twice a day, Group B (controls) was continued on their maximum tolerated background treatment and placebo. Patient were called for follow up at 12 weeks and reassessed in terms of angina attacks per week. All data was recorded on specially designed performa and confidentiality of the data was ensured.

STATISTICAL ANALYSIS:

Collected data was analyzed by SPSS version 21.0. Numerical variable i.e. age, angina attacks per week from baseline were summarized as mean and standard deviation. Qualitative variables like gender were presented in the form of frequency and percentages. Independent t-test was used to see the comparison of number of anginal attacks between both groups. Data was stratified for age, duration of disease and gender and pre and post stratification t-test was used to assess number of angina attacks in both groups with p value <0.05 used as significant value.

RESULTS:

There were 256 patients with mean age of 49.5 ± 6.8 years having 150 (58.5%) males and 106 (41.5%) females. The baseline demoghraphic characteristics of both groups were comparable (table 1). The efficacy of trimeatazidine was superior to other drugs i.e number of attacks reduced from 5.06 ±2.0 to 3.6±2.2 in TMZ group as compared to 5.5 to 5.4 in control group. p value was not significant at start of study i.e. 0.150. p value got significant at the end of study i.e. 0.000. (table 2)

Data stratification was done between age of patient and efficacy of trimetazidine in terms of mean and standard deviation of angina attacks i.e in elder age group number of attack at start of study was 5± 1.90 in group A which reduced to 3.6 ± 2.0 at end of study. while in younger age group number of attack at start of study in Group A was 5.80 ± 2.8 which reduced to 4.3 ± 3.6 in group

Table 1: Baseline characteristic of sampled population

		Group		Total
		Group A	Group B	
Age		49.16±6.6	49.93±7.1	49.5±6.8
Age group	18-39 years	10 (7.8%)	8 (6.2%)	18 (7%)
	40-60 years	118 (92.2%)	120 (93.8%)	238 (93%)
Gender	Female	50 (47.2%)	56 (52.8%)	106 (100%)
	Male	78 (52%)	72 (48%)	150 (100%)
Diabetes		40 (31.2%)	52 (40.6%)	92 (35.5%)
Hypertension		24 (18.8%)	51 (39.8%)	75 (29.3%)
Smoking		35 (27.3%)	35 (27.3%)	70 (27.3%)

Table 2: Comparison of angina attack in both groups at start and end of study

	Group	N	Mean	Std. Deviation	Std. Error Mean	p-value
Angina attack at start of study	Group A	128	5.06	2.038	.180	0.150 Not significant
	Group B	128	5.53	3.056	.270	
Angina attack at end of study	Group A	128	3.66	2.215	.196	0.000 significant
	Group B	128	5.42	2.619	.232	

Table 3: Data stratification in Group A

Gender						
	Gender	N	Mean	Std. Deviation	Std. Error Mean	p-value
Angina attack at start of study	Female	50	5.32	2.1	.304	0.254
	Male	78	4.90	1.9	.222	
Angina attack at end of study	Female	50	3.78	2.1	.297	0.619
	Male	78	3.58	2.2	.260	
Age groups						
Angina attack at start of study	40-60 year	118	5.00	1.9	.180	0.235
	18-39 year	10	5.80	2.8	.904	
Angina attack at end of study	40-60 year	118	3.60	2.0	.190	0.340
	18-39 year	10	4.30	3.6	1.165	
Diabetes						
Angina attack at start of study	Yes	40	4.88	1.7	.275	0.485
	No	88	5.15	2.1	.231	
Angina attack at end of study	Yes	40	3.15	1.7	.281	0.081
	No	88	3.89	2.3	.252	
Hypertension						
Angina attack at start of study	Yes	24	5.08	1.6	.340	0.956
	No	104	5.06	2.1	.208	
Angina attack at end of study	Yes	24	4.25	2.1	.431	0.146
	No	104	3.52	2.2	.218	
Smoking						
Angina attack at start of study	Yes	35	4.71	1.9	.324	0.237
	No	93	5.19	2.0	.215	
Angina attack at end of study	Yes	35	3.49	2.2	.385	0.595
	No	93	3.72	2.1	.228	

Table 4: Data stratification in Group B

	Gender	N	Mean	Std. Deviation	Std. Error Mean	p-value
Gender						
Angina attack at start of study	Female	56	5.45	2.8	.380	0.783
	Male	72	5.60	3.2	.380	
Angina attack at end of study	Female	56	5.41	2.4	.327	0.966
	Male	72	5.43	2.7	.326	
Age group						
Angina attack at start of study	40-60 year	120	5.50	3.1	.285	0.656
	18-39 year	8	6.00	1.8	.655	
Angina attack at end of study	40-60 year	120	5.41	2.6	.244	0.822
	18-39 year	8	5.63	1.7	.625	
Diabetes						
Angina attack at start of study	Yes	52	5.29	2.7	.387	0.459
	No	76	5.70	3.2	.371	
Angina attack at end of study	Yes	52	5.38	2.4	.334	0.895
	No	76	5.45	2.7	.318	
Hypertension						
Angina attack at start of study	Yes	51	5.45	3.3	.462	0.810
	No	77	5.58	2.9	.331	
Angina attack at end of study	Yes	51	5.31	2.4	.342	0.705
	No	77	5.49	2.7	.312	
Smoking						
Angina attack at start of study	Yes	35	5.71	3.1	.539	0.679
	No	93	5.46	3.0	.313	
Angina attack at end of study	Yes	35	5.46	2.6	.450	0.926
	No	93	5.41	2.6	.271	

at end of study. While in placebo group there was no significant difference and p value was 0.6 at start of study and 0.8 at the end of study.

Data stratification was done between gender and efficacy of trimetazidine in term of mean and standard deviation of angina attacks i.e in male group number of attacks at start of study was 4.9 ± 1.9 which reduced to 3.5 ± 2.2 and in females it reduced from 5.3 ± 2.1 to 3.7 ± 2.1 in TMZ group, while there was no significant reduction in placebo group. (table 3 and 4).

Data stratification was done for Diabetes, hypertension, and smoking and TMZ was equally effective in all groups. (table 3 and 4)

DISCUSSION:

The last two decades have witnessed dramatic changes regarding chronic stable angina treatment. From the conservative strategy and few therapeutic medications, there has evolved a multifaceted strategy comprising pharmacological agents like trimetazidine as monotherapy. Trimetazidine (TMZ) can improve myocardial ischemia due to its metabolic activity as evident in international studies but local data is not sufficient in regard the efficacy in local population of Pakistan. This study was conducted to assess the effectiveness of trimetazidine in our setup. In our study the efficacy of trimeatazidine was superior to other drugs i.e number of attacks reduced in TMZ group as compared to placebo group which shows very limited improvement. This result is similar to other studies. A meta-analysis comparing data from 1985 to 2001 was carried out to see the effectiveness of trimetazidine as a single agent or in combination with other anti anginal medications and a total of 12 studies were included. Only double-blind, randomized, controlled trials were included in this meta-analysis. Patients received treatment with trimetazidine for 15 days and four parameters were selected, one clinical parameter (i.e. number of weekly angina attacks) and three ergometric parameters (i.e. time to 1 mm ST-segment depression, total work and exercise duration at peak exercise). These parameters were evaluated at the start and then at the end of study period. Standard statistical methods, pooled odds ratio and 95% confidence intervals for subjective symptoms and pooled z and P for objective symptoms were used. Results indicated that TMZ reduced the frequency of weekly anginal attacks and there was improvement in the time to 1 mm segment depression and total work at peak exercise, while exercise duration at peak exercise revealed a tendency toward improvement $(P = 0.09)$.[6]

In another international study TRIADA the primary objective was to evaluate the efficacy and tolerability of trimetazidine at 35 mg twice daily dose which was added to current therapy involving the maximum of two anti-anginal drugs. The outcome was evaluated after 12 weeks of therapy and compared with baseline data. The study included 74 patients with stable exertional angina pectoris (AP) TRIADA confirmed that the use of trimetazidine in a new pharmacological form is effective and well tolerated in the treatment of angina.[7]

In a multicentre study trimetazidine was compared with placebo and found more efficacious than placebo in term of reduced angina attack per week. The number of angina episodes per week reduced from a mean of 5.6 ± 0.6 to 2.7 ± 0.5 versus 6.8 ± 0.7 to 5.1 ± 0.7 (in the TMZ group vs in the Placebo group), $(P < 0.05)$.[8]

In another international study which compared propranolol and trimetazidine, there was no noticeable differences (mean difference P-TMZ: 2; 95% CI: -4.4, 0.5). This difference can be due to smaller sample size of that study i.e 149, while our sample

size is larger i.e 256 [9] our result is strengthens by another study in which mean weekly number of angina episodes in TMZ cohort at the start of study was 4.0 ± 3 which reduced to 2.1 ± 2 at the end of study while in placebo group baseline number of attack per week were 4.2 ± 4.[10]

Our data have showed, the mean age of patient is 49.5 ± 6.6 while in international study the mean age of patients were 58 ± 1 for trimetazidine group and 57 ± 1 for other group. Which is almost equal to our study and results of efficacy are also comparable. 9 In another study The mean age of TMZ group was 54.5 ± 8 and in placebo group mean age was 54.2 ± 8. [10]

In our study the duration of disease was calculated in weeks which was 12 to 33 week in 222 patients and 34 to 54 week in remaining patients while duration of angina pectoris in other comparative study was calculated in months i.e for trimetazidine was 52 ± 7 and for other group 46 ± 8(months). This difference can be due to earlier presentation of patients now a day as compared to past. So earlier the treatment started better is the response and less number of complications.[9] in an international study the duration of angina was calculated in months 57.6 ± 5 in TMZ group and 58.7 ± 5 in placebo group.[10]

In our study the number of male patient is 150 while 106 were female patients. In another study there were similarly greater number of male patients i.e 142 in TMZ group and 137 in placebo group while lesser number of female patients i.e 37 in TMZ group and 31 in placebo group which indicates more prevalence of disease among male patients. It can also be due to better health access in male patient as compared to female patients.[10]

CONCLUSION:

The addition of Trimetazidine as an add-on treatment may be beneficial to reduce angina episodes.

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