Original Article

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Effect of Ranolazine in Patients with Chest Pain and Normal Coronaries- A Hospital Based Study

Internal Medicine Section

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ABSTRACT

Introduction: There is an important role of coronary microcirculation in the clinical presentation and prognosis of patients who have typical chest pain despite normal epicardial coronary arteries (microvascular angina). Treatment of these patients is empirical because of the incomplete knowledge of its cause. Limited data has shown that ranolazine reduces angina and improves exercise performance in such patients with frequent angina.

Aim: To evaluate the effect of ranolazine in patients with chest pain and normal epicardial coronaries (micro-vascular angina).

Materials and Methods: Sixty-five patients with anginal symptoms with abnormal exercise stress test and normal epicardial coronaries were enrolled for the study. All participants had baseline demographic and health history questionnaires, including Seattle Angina Questionnaire (SAQ) and Duke Activity Status Index (DASI). After enrolment, patients were randomly divided into two groups. One group (group 1) was assigned to ranolazine for six weeks along with other indicated anti-anginal drugs. The other group (group 2) was assigned to anti-anginal drugs other than ranolazine. Patients were reassessed for symptomatic and functional improvement (SAQ, DASI) at six weeks.

Results: Mean age of patients examined were 49.03 years in group 1 and 49.77 years in group 2. Approximately 42.9% of patients in group 1 and 40% in group 2 were male. Despite current anti-anginal therapy, patients in both the groups were symptomatic. At six weeks, 60% of patients in group 1 had angina as compared to 88.6% at baseline ($p<0.05$). Similarly, scores of domains of SAQ were higher at six weeks as compared to baseline ($p<0.05$) except for treatment satisfaction. No improvement of DASI score and functional capacity were seen in either group at six weeks as compared to baseline ($p>0.05$). At six weeks, angina was significantly lower in group 1 as compared to group 2 (60 % vs 86.7%; $p<0.05$). Four out of five SAQ subscale score were higher in ranolazine group as compared to the other group ($p<0.05$). Treatment satisfaction trended lower on ranolazine group ($p<0.05$). There was no significant differences in DASI in the two groups (DASI score 30.59 vs 29.85, $p>0.05$).

Conclusion: Ranolazine is safe and improves symptoms significantly in patients with micro-vascular angina.

Keywords: Anti-anginal drugs, Epicardial coronaries, Microvascular angina

INTRODUCTION

Although the association between myocardial ischaemia and atherosclerotic coronary artery disease is well-known, several previous studies have demonstrated the importance of coronary microcirculation in the clinical presentation and prognosis of patients presenting with typical chest pain despite normal epicardial coronaries in angiogram (Micro-Vascular Angina {MVA}) [1]. As the knowledge regarding the aetiology of MVA is limited, treatment of such patients is largely empirical [2].

Patients with persisting symptoms despite optimal anti-ischaemic drug therapy, several alternative forms of treatment have been proposed. Ranolazine is an anti-anginal drug shown to reduce angina and improve exercise performance in selected patients with positive exercise testing and normal epicardial coronaries with frequent angina. It is proposed that ranolazine causes maintenance of sodium-calcium homeostasis by reducing sodium entry into myocardial cells through sodium channels [3]. The current study was aimed at evaluating the efficacy of ranolazine in patients with micro-vascular angina.

MATERIALS AND METHODS

This prospective observational study was carried out from August 2015 to July 2016.

Sixty-five patients with anginal symptoms (or angina equivalent) with abnormal exercise stress test and normal epicardial coronaries were enrolled for the study.

Inclusion criteria:

- Anginal chest pain or dyspnoea on exertion;
- Abnormal routine exercise stress testing;
- No obstructive Coronary Artery Disease (CAD) (<50% epicardial coronary stenosis in all epicardial coronary arteries).

Exclusion criteria:

- Patients younger than 18 years of age;
- Hepatic insufficiency, prolonged QT interval, renal failure;
- Use of drugs that inhibit CYP3A such as diltiazem, verapamil, ketoconazole, macrolides and protease inhibitors;
- Patients taking drugs that prolong QT interval;
- Pregnancy or breastfeeding;
- Parkinson's disease;
- Life expectancy <6 months.

Written informed consent was taken from all subjects before study participation. The study was approved by the Ethical Committee of the Institute. Baseline screening 12-lead Electrocardiogram (ECG), 2D echocardiogram for left ventricular ejection fraction and regional wall motion abnormality and routine blood investigation was done in each patient. All participants had baseline demographic and health history questionnaires, including Seattle Angina Questionnaire (SAQ) and Duke Activity Status Index (DASI). After enrollment in the study, patients were randomly divided into two groups. One group

of participants (Group 1, n=35) was assigned to ranolazine 500 mg orally twice daily for two weeks and then 1,000 mg twice daily (as per US FDA, Feb 2003) for an additional 4weeks along with other indicated anti-anginal drugs. The other group of participants (Group 2, n=30) were on the usual prescribed anti-anginal drugs other than ranolazine. It was ensured that the participants' usual anti-anginal medication regimen remained unchanged in both the groups throughout study duration. Patients were reassessed for symptomatic and functional improvement (SAQ, DASI) at six weeks in both groups and results were compared. The SAQ is a self-administered, 19-item questionnaire. It measures five dimensions of anginal symptoms like physical functioning, angina stability, angina frequency, treatment satisfaction and quality of life. Scores range from 0-100 in each domain, with higher scores indicating better levels of functioning. Similarly, DASI is a 12-item self-administered questionnaire having specific points for each activity with total 58.2 points (DASI score). Functional capacity in Metabolic Equivalents (METS) is calculated by the formula

Functional Capacity in METS = (DASI score) x 0.43+9.6 then divide by 3.5

STATISTICAL ANALYSIS

Continuous variables were calculated by two sample t-test. The significance (p-value) of the variables during follow-up was calculated by Z-test using Statistical Package for the Social Sciences (SPSS) software.

RESULTS

Sixty-five patients after enrollment were divided in to two groups. Group 1 (n=35) were assigned to ranolazine in addition to usual anti-ischaemic therapy and group 2 (n=30) were assigned to only usual anti-ischaemic therapy.

Baseline characteristics of patients in group 1 & 2 are shown in [Table/Fig-1].

Despite current anti-anginal therapy, majority of patients in both groups were symptomatic [Table/Fig-1]. Mean DASI score with functional capacity and mean scores in the five domains of SAQ in group 1 and 2 at baseline is shown in [Table/Fig-1].

At six week, patients in group 1 had significant reduction in angina symptoms as compared to baseline [Table/Fig-2]. Similarly, domains of SAQ were significantly better in group 1 at six weeks except treatment satisfaction which was significantly less. [Table/Fig-2].

Symptomatic and functional status along with the domains of SAQ in group 2 at six weeks as compared to baseline is also shown in [Table/Fig-2].

Comparison between two groups at six weeks

After six weeks, patients in group 1 had significant reduction in anginal symptom as compared to group 2 ($p<0.05$) [Table/Fig-3].

Moreover, four out of five SAQ subscale score were higher in ranolazine group as compared to the other group ($p<0.05$). However, mean DASI score and functional capacity in group 1 and 2 after six weeks did not show significant difference. [Table/Fig-3].

DISCUSSION

Although MVA is not discernible from angina of obstructive CAD, it persists longer after exertion and shows poor response to nitroglycerin [4,5]. Exercise ECG and scintigraphic stress tests also are not remarkable for its diagnosis. However, appearance of angina or ST-T changes occurring during echocardiography stress test may suggests MVA [6,7]. Similarly, earlier appearance of ECG changes or angina during exercise test with sublingual nitrate administration may also give clue towards MVA [8].

Prevalence of microvascular dysfunction is more common in female as compared to male. Moreover, pain may be disabling in women

Variables	Group 1(n=35)	Group 2 (n=30)	p-value
Mean age (years)	49.03	49.77	0.573
Male	15 (42.9%)	12 (40%)	0.8157
Risk Factors			
Hypertension	13 (37.1%)	11 (36.7%)	0.968
Diabetes	4 (11.4%)	7 (23.3%)	0.201
Dyslipidemia	10 (28.6%)	9 (30%)	0.899
Smoking	8 (22.9%)	6 (20%)	0.779
Symptoms (%)			
Angina	31 (88.6%)	26 (86.7%)	0.815
Dyspnoea	9 (25.7%)	7 (23.3%)	0.824
DASI Score	28.98	29	0.982
Functional capacity (METS)	6.28	6.28	1
Seattle Angina Questionnaire (SAQ)			
Physical functioning	84.4	84.4	0.948
Angina stability	51.3	51.3	0.978
Angina frequency	70.8	70.2	0.437
Treatment satisfaction	91.3	89.7	0.030
Quality of life	66.7	65.4	0.064

[Table/Fig-1]: Baseline characteristics of two groups.

Variables	Group 1 (n=35)			Group 2 (n=30)		
	Baseline	At six weeks	p-value	Baseline	At six weeks	p -value
Angina	31 (88.6%)	21 (60%)	<0.05	26 (86.7%)	26 (86.7%)	1
Dyspnoea	9 (25.7%)	5 (14.3%)	0.27	7 (23.3%)	5 (16.7%)	0.52
DASI	28.98	30.59	0.07	29	29.85	0.37
Functional capacity (METS)	6.28	6.47	0.08	6.28	6.38	0.39
SAQ:						
Physical functioning	84.4	90.91	<0.05	84.43	85.43	0.053
Angina stability	51.3	74.03	<0.05	51.33	55.23	<0.05
Angina frequency	70.8	85.51	<0.05	70.27	76.03	<0.05
Treatment satisfaction	91.31	85.26	<0.05	89.73	89.07	0.22
Quality of life	66.7	75.73	<0.05	65.43	70.8	<0.05

[Table/Fig-2]: Comparison in each group before and after starting treatment (baseline and six weeks).

Variables	Group 1(n=35)	Group 2 (n=30)	p-value
Angina	21 (60%)	26 (86.7%)	0.016
Dyspnoea	5 (14.3%)	5 (16.7%)	0.790
DASI Score	30.59	29.85	0.385
Functional capacity (METS)	6.47	6.38	0.397
SAQ			
Physical functioning	90.91	85.43	<0.05
Angina stability	74.03	55.23	<0.05
Angina frequency	85.51	76.03	<0.05
Treatment satisfaction	85.26	89.07	<0.05
Quality of life	75.71	70.8	<0.05

[Table/Fig-3]: Comparison between two groups at 6 weeks.

and there are unpredictable responses with use of conventional anti-ischemic therapy [2]. Women with signs and symptoms of myocardial ischaemia often have no obstructive CAD by invasive coronary angiography when compared to men. NHLBI WISE study demonstrated that approximately 50% of women with symptoms of persistent chest pain, evidence of ischaemia and presence of no obstructive CAD, have microvascular dysfunction [9]. In the present study also, almost two third of the patients (60%) were female with persistent symptoms.

In our study, hypertension and dyslipidaemia were present in about one third of patients in both the groups. However, diabetes and history of smoking were less common and there was no statistical difference between the two groups. As per characterization of MVA, no cardiac or systemic diseases should be apparent in these patients. However, patients with uncomplicated hypertension

or diabetes mellitus are included as they are considered as risk-factors for coronary microvascular dysfunction like in coronary atherosclerosis [1,10].

Despite current medications, all the patients in both groups were symptomatic at baseline, angina on exertion being the most prominent symptom. As per literature, patients with microvascular dysfunction present with angina episodes that are primarily related to effort. At baseline, symptom and functional status (DASI and SAQ) in the two groups were comparable. In this study, we compared angina symptoms and functional status after six weeks of treatment, in the group taking ranolazine with the group not taking the same, using SAQ and DASI. The SAQ questionnaire is well validated in stable coronary heart disease patients [11]. It provides important information for patients with angina. Higher scores indicate better levels of functioning and quality of life. Similarly, DASI has also been validated as a measure of functional capacity [12]. Angina and thereby ischaemia predict adverse cardiovascular events in patients with and without obstructive CAD [9,13,14]. Ranolazine has been established as an effective anti-anginal drug in patients with obstructive CAD and there is evidence that it improves ischaemia [15]. In our study, patients with angina, evidence of ischaemia and no obstructive CAD had significant benefit from ranolazine compared to patients without ranolazine. At six weeks, angina symptoms were significantly lower in the group of patients taking ranolazine. Similarly, scores of domains of SAQ were higher at six weeks as compared to baseline. While comparing the two groups at six weeks, angina was significantly lower in ranolazine group as compared to no ranolazine group. SAQ sub-scale score were also higher in ranolazine group as compared to the other group. However, treatment satisfaction trended in a negative direction on ranolazine. This may be because of patients' expectation that ranolazine would provide a complete relief of angina or could be related to side-effects of ranolazine, although all subjects completed the study period with no drop-outs. Previous studies like Chaitman et al., (CARISA study) showed that ranolazine improved symptoms of myocardial ischaemia and quality of life in patients with MVA. The CARISA study also demonstrated that addition of ranolazine in women had similar reductions in angina frequency and nitroglycerin use as in men [16]. Similarly, analysis from the MERLIN–TIMI 36 study showed that women had less obstructive CAD compared with men and had 29% reduction in recurrent ischaemia on ranolazine compared with placebo [17].

LIMITATION

Our study was conducted enrolling a small number of patients in either group over a short period of time. Therefore this is limited, with regard to definitive statement, regarding the role of ranolazine as anti-ischaemic therapy in patients with MVA. Moreover, the potential for influence on certain aspects of our study design remain plausible including patient familiarity with the treatment protocol, which remains unaccounted for in our data analysis. Thirdly, although SAQ measures chest pain and shortness of breathe to evaluate angina, many patients with ischaemia experience anginal equivalents such as fatigue, indigestion, and weakness which cannot be measured by SAQ.

CONCLUSION

In MVA patients with persistent symptoms, despite optimal anti-ischaemic drug therapy, several alternative forms of treatment have been proposed. As novel anti-anginal, anti-ischemic medication, ranolazine is safe, well tolerated and improves symptoms in patients with MVA.

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