Research Paper

Antianginal Efficacy and Tolerability of Ranolazine as an Add-on Drug to Concomitant Medications Primarily Metoprolol in Chronic Stable Angina Patients: A Prospective, Open-Label Study

Anant Mahaveer Khot, H. V. Anuradha[1], V. S. Prakash[2], M. C. Shivamurathy[1]

Department of Pharmacology, BLDEU's Shri B. M. Patil Medical College and RC, Vijayapura, [1]Department of Pharmacology, M. S. Ramaiah Medical College, [2]Department of Cardiology, M. S. Ramaiah Medical College, Bengaluru, Karnataka, India

Abstract

Objective: To evaluate the efficacy and tolerability of ranolazine as an add-on drug in chronic stable angina patients and the impact of ranolazine on the quality of life in chronic stable angina patients receiving other antianginal medications. **Materials and Methods:** It was a prospective, open-label, hospital-based study involving 144 patients with chronic stable angina. First group received either metoprolol 12.5 or 25 mg/day or other antianginal medications; if the symptoms persist, the dose of metoprolol was increased to 50 mg/day, and to the second group, ranolazine 500 mg BD or 1 g OD was added along with metoprolol or others if the anginal attacks were not subsiding. The patients were followed up to 6 months with electrocardiography, treadmill test, and quality of life questionnaire. Adverse events were recorded at each visit during the study. **Results:** There was a statistically significant reduction in weekly anginal frequency ($P < 0.001$) and improvement in an exercise tolerance in both the groups, but more in the ranolazine group. Adverse events reported were mild, infrequent. **Conclusion:** Ranolazine is could be used as an add-on drug in chronic angina patients not improved with metoprolol or antianginal medications.

Keywords: Coronary artery disease, exercise tolerance, percutaneous intervention, quality of life, ranolazine

Introduction

Coronary heart disease (CHD) is the leading cause of death in India and worldwide. The Global Burden of Disease study estimate of age-standardized cardiovascular disease (CVD) death rate of 272/100,000 population in India is higher than the global average of 235/100,000 population. Premature mortality in terms of years of life lost because of CVD in India increased by 59%, from 23.2 million (1990) to 37 million (2010).[1]

Chronic stable angina is the major symptomatic presentation in about 50% of CHD patients. There is a growing prevalence of chronic ischemia and angina due to residual coronary artery disease after percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG). Despite optimal revascularization, nearly 80% of the patients in the PCI group and 60% in the CABG group continued to experience angina and require antianginal medications.[2]

Ranolazine, a piperazine derivative, is relatively new antianginal drug.[3] It exhibits its antianginal effect without eliciting any change in the heart rate, blood pressure, or rate pressure product, as compared to beta-blockers and calcium channel blockers. A *post hoc* analysis of diabetic patients in the CARISA trial reported not only a reduction in the mean number of anginal episodes per week but also a reduction in the glycated hemoglobin levels by 0.72 from the baseline.[4] Despite all these peculiarities, studies relating to its use as an antianginal drug (both monotherapy or in combination)[5]

Address for correspondence: Anant Mahaveer Khot, Department of Pharmacology, BLDEU's Shri B. M. Patil Medical College and RC, Vijayapura - 586 103, Karnataka, India.
E-mail: anantkhot04@gmail.com

Access this article online

Quick Response Code:

Website: www.jpharmacol.com

DOI: 10.4103/jpp.JPP_168_16

How to cite this article: Khot AM, Anuradha HV, Prakash VS, Shivamurathy MC. Antianginal efficacy and tolerability of ranolazine as an add-on drug to concomitant medications primarily metoprolol in chronic stable angina patients: A prospective, open-label study. J Pharmacol Pharmacother 2017;8:21-7.

Received: 28-10-2016 **Revised:** 29-12-2016 **Accepted:** 20-01-2017

among Indian patients were only a few; hence, this study was undertaken with the following objectives:

1. To evaluate the efficacy and tolerability of ranolazine as an add-on drug in chronic stable angina patients
2. To study the impact of ranolazine on the quality of life in chronic stable angina patients receiving other antianginal medications.

Materials and Methods

It was a prospective, open-label, hospital-based study involving 144 patients (both ranolazine and metoprolol group) with chronic stable angina, who attended the Cardiology Department at M. S. Ramaiah Medical College Hospital after November 2010.

The study participants were recruited based on following inclusion and exclusion criteria; written informed consent was obtained from all the patients and Institutional Ethics Committee approval was sought before performing the study.

Inclusion criteria

1. Patients of either sex with age ≥18 years, diagnosed to be having chronic stable angina
2. Chronic stable angina of ≥3 months and ≥2–3 episodes of angina per week during a ≥2-week qualification period despite treatment treatment with metoprolol 25 mg OD/BD.

Exclusion criteria

1. Patients will be excluded if they have New York Heart Association functional Class IV congestive heart failure
2. An episode of myocardial infarction or unstable angina within the previous 2 months
3. Active acute myocarditis, pericarditis, hypertrophic cardiomyopathy, uncontrolled hypertension
4. Patients with history of torsades de pointes and those receiving agents that are known to prolong QT_c interval
5. Patients with creatinine clearance <30 ml/min or chronic illnesses those are likely to interfere with protocol compliance.

Sample size

Sample size was calculated using the formula for assessing the difference between the means by nMaster software (ranolazine group and metoprolol group) from the ERICA trial.[6] Required sample size in each group was 72 to have a power of 90%.

The first group received either metoprolol 12.5 mg OD/BD or other antianginal medications [Table 1]; if the symptoms persist, the dose of metoprolol was gradually increased to a maximum dose as 100 mg OD(50 mg BD), or similarly, the doses of other antianginal drugs were also increased.

The second group received ranolazine 500 mg BD/1 g OD if chronic stable angina of ≥3 months and ≥2–3 episodes of angina per week during a ≥2-week qualification period despite treatment with metoprolol 25 mg OD/BD or recommended dose of other antianginal medications. The flow of study sequence was as shown in Figure 1.

Study sequence

Parameters measured

1. Weekly angina frequency
2. Exercise tolerance by performing treadmill test (TMT).

Investigations performed

1. Electrocardiography (ECG)
2. TMT.

Results were interpreted by using both Bruce and modified Bruce protocol.[7]

Follow-up

Patients were followed up for 6 months. ECG, exercise tolerance test, and the administration of pretested structured questionnaire Seattle Angina Questionnaire (SAQ)[8] were performed at the baseline and at the end of 2 months. At the end of 6 months, a stress ECG by TMT and administration of SAQ were repeated. Results were tabulated and statistical analysis was done.

Statistical analysis

It was done by using SPSS 23, IBM obtained from SPSS South Asia Private limited, Bangalore, India. Descriptive and inferential statistical analysis has been carried out in the present study. Results of continuous variables are presented as mean ± standard deviation and of categorical variables are expressed as percentages. Student's *t*-test (two-tailed, independent) has been used to find the significance of study parameters on a continuous scale between two groups. Chi-square test was used for qualitative data.

Results

This study was started from November 2010 with an intent to know the efficacy of ranolazine as an add-on drug to

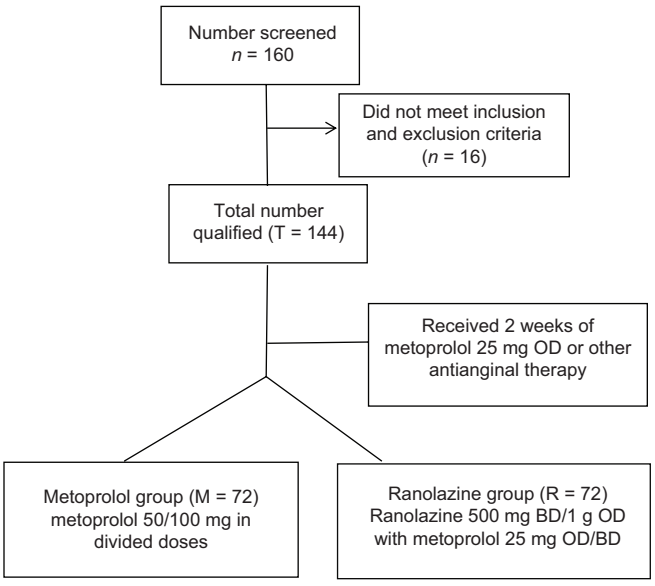

Figure 1: Flow of participants through the trial

concomitant antianginal medications, primarily metoprolol in Indian patients. A total of 144 patients were enrolled in the study and baseline characteristics of both groups are summarized in Table 2.

Mean anginal frequency per week in both the groups at baseline and at the end of 2 and 6 months is shown in Figure 2. In both the groups, there was statistically significant reduction in frequency of angina per week at the end of 2 months ($P < 0.001$). However, at the end of 6 months, reduction in anginal frequency was more significant in ranolazine group as compared to metoprolol group.

Exercise tolerance by TMT was performed at baseline and at the end of 2 and 6 months. Figure 3 depicts the mean duration of exercise performed by the patients in both the groups either using Bruce or modified Bruce protocol. At baseline and at the end of 2 months, mean duration of exercise performed in both the groups was different statistically ($P < 0.002$). At the end of 6 months, the difference was not significant ($P < 0.062$). When assessed for exercise tolerance at baseline and at the end of 2 and 6 months within metoprolol and ranolazine group separately (intragroup analysis), it was found statistically significant in both the groups ($P < 0.001$).

Quality of life was assessed using SAQ, but the results which are not included in the analysis because of absence of follow-up data on quality of life in few patients in both the groups and complexity of analysis of data derived from it and the adverse events reported during the study are summarized in Table 3.

Table 1: Distribution of different class of antianginal drugs in two groups of patients studied

Drugs	Metoprolol group ($n=72$), n (%)	Ranolazine group ($n=72$), n (%)
Nitrates	12 (16.7)	23 (31.9)
Beta-blockers	62 (86.1)	47 (65.2)
Metoprolol	4 (5.6)	8 (11.1)
Metoprolol extended release tablets	32 (44.4)	26 (36.1)
Fixed drug combinations of metoprolol	19 (26.3)	7 (9.7)
Atenolol	6 (8.3)	3 (4.1)
Bisoprolol	1 (1.3)	1 (1.3)
Nebivolol	2 (2.7)	2 (2.7)
Carvedilol	1 (1.3)	5 (6.9)
Calcium channel blockers	14 (19.4)	16 (22.2)
ACE inhibitors	17 (23.6)	14 (19.4)
ARBs	8 (11.1)	11 (15.2)
Fixed drug combinations of ARBs	11 (15.2)	6 (8.3)
Metabolic modulators	3 (4.1)	72 (100.0)
Novel agents	15 (20.8)	34 (47.2)
Antiplatelet agents	21 (29.1)	26 (36.1)
Fixed drug combinations of antiplatelet agents	52 (72.2)	48 (66.7)
Statins	68 (94.4)	70 (97.2)

ACE=Angiotensin-converting enzyme, ARBs=Angiotensin receptor blockers

Discussion

Our findings show that when compared ranolazine as add-on drug with metoprolol in patients with chronic stable angina who were not controlled on monotherapy has proven to be safe and effective option.

Ranolazine has reduced mean anginal frequency, but the exercise tolerance as assessed by mean duration of exercise on TMT has shown statistically significant difference at baseline and at the end of 2 months and shown comparable result at the end of 6 months. One reason why it was significant at the end of 2 months but not at the end of 6 months could be due to the difference in exercise tolerance at the baseline ($P < 0.002$) and the adverse events reported during study period were infrequent and minor once.[9] No serious adverse events[10] were reported during the study period. It was really difficult to assess for the causality[11] as patients in both the groups were taking ≥2 medications. Findings of this study are consistent with ERICA

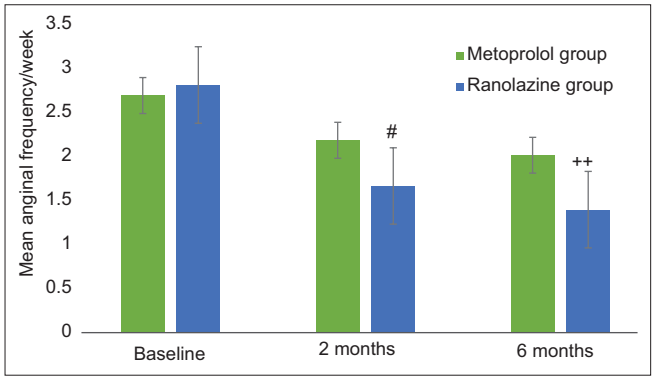

Figure 2: Mean anginal frequency of the study groups. #Statistically significant difference in both groups from baseline to 2 months ($P < 0.001$). ++ Significant reduction in ranolazine group at the end of 6 months ($P < 0.001$)

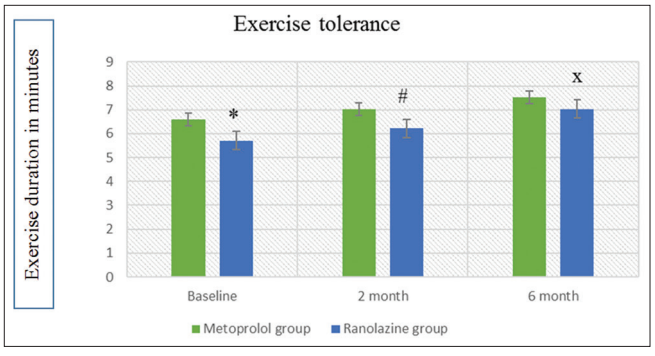

Figure 3: Exercise tolerance by treadmill test. *Statistically significant difference at baseline. #Statistical significant difference in exercise tolerance between 2 groups at the end of 2 months ($P = 0.002$). xExercise tolerance was not significant statistically at the end of 6 months ($P = 0.062$)

Table 2: Baseline characteristics

Variables	Metoprolol group ($n=72$)	Ranolazine group ($n=72$)	*P*
Age (years), mean±SD	56.79±8.69	60.69±10.74	0.018*
Gender			
Male/women (%)	73.6/26.3	70.8/29.1	0.853
Anginal frequency/week	2.70±3.13	2.82±2.41	0.952
Exercise tolerance	6.60±1.97	5.70±1.41	0.002*
SAQ score, mean±SD			
Physical limitation	4.80±0.47	4.72±0.50	0.396
Angina stability	3.14±1.23	2.98±1.03	0.449
Anginal frequency	4.98±1.07	4.46±1.30	0.024*
Treatment satisfaction	4.12±0.60	3.99±0.55	0.230
Disease perception	3.98±0.94	3.87±0.93	0.531
Medical history of, *n* (%)			
Diabetes mellitus	29 (40.27)	40 (55.55)	0.06
Hypertension	43 (59.72)	33 (45.83)	0.09
Previous PCI	9 (39.13)	14 (60.87)	0.25
Previous CABG	2 (28.57)	5 (71.43)	0.24

*Statistically significant difference between both the groups - $P<0.05$. CABG=Coronary artery bypass graft, PCI=Percutaneous coronary intervention, SD=Standard deviation, SAQ=Seattle Angina Questionnaire

Table 3: Adverse events reported during the study

M group - adverse events	Number of patients	R group - adverse events	Number of patients
Retrosternal burning	2	Nausea	1
Itching + rash	1	Gastric irritation	2
Diarrhea	1	Cough + edema	1
Exhaustion	1	Headache	1
Insomnia	1	Giddiness	1
Headache	1	Dyspnea	1
Restlessness	1	Backache	1
Asthenia	1	Constipation	1
Weight loss	1		

trial which was conducted to know the efficacy of ranolazine as an add-on drug to calcium channel blockers.

In our study, we had nine patients in metoprolol group and 14 patients in ranolazine group who underwent PCI previously. Few patients underwent PCI during the follow-up visit and they received ranolazine perioperatively.

Strength of the study

Large sample size and long duration of follow-up are the strengths of the study.

Limitations of the study

Hospital-based study – sample what we get is not representative of whole Indian population.

Effect of ranolazine on quality of life was not assessed.

Another important problem with our patients was lack of compliance to therapy (on polypharmacy usually) and had multiple risk factors for CHD. Hence, the treating cardiologists preferred PCI (patients had multiple government schemes and insurances) over the trial of multiple medications and follow it for their efficacy and safety as it was concluded in the study conducted by Wijeysundera *et al*.[12] and opposite of COURAGE trial which states that there is no difference in survival between an initial strategy of PCI plus medical therapy and medical therapy alone in patients with stable ischemic heart disease.[13] Further well-designed randomized trials with meta-analysis are required to prove the efficacy of ranolazine.

Conclusion

According to our study, ranolazine was justified for use as an augmenting agent[14] in combination with other antianginal drugs primarily metoprolol in chronic stable angina patients but not as monotherapy as it was concluded in MARISA trial.[15]

Acknowledgment

We would like to thank Dr. Sathyendra Kashyp, Dr. Mukunda N R and Dr. Niveditha for support.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Prabhakaran D, Jeemon P, Roy A. Global burden of cardiovascular disease cardiovascular diseases in India. Circulation 2016 Apr 18;133(16):1605.
2. Boden, WE. Medical management of stable coronary artery disease. In: Cairns JA, Gersh BJ, editors. Evidence-Based Cardiology. 3rd ed. London: John Wiley and Sons; 2011. p. 345-53.
3. Antman EM, Selwyn AP, Loscalzo J. Ischemic heart disease. In: Long DL, Kasper DL Jameson JL, Fauci AS, Hauser SL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill; 2012. p. 2000-13.
4. Chaitman BR, Pepine CJ, Parker JO, Skopal J, Chumakova G, Kuch J, *et al.* Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: A randomized controlled trial. JAMA 2004; 291:309-16.
5. Klein WW, Jackson G, Tavazzi L. Efficacy of monotherapy compared with combined antianginal drugs in the treatment of chronic stable angina pectoris: A meta-analysis. Coron Artery Dis 2002;13:427-36.
6. Stone PH, Gratsiansky NA, Blokhin A, Huang IZ, Meng L; ERICA Investigators. Antianginal efficacy of ranolazine when added to treatment with amlodipine: The ERICA (Efficacy of Ranolazine in Chronic Angina) trial. J Am Coll Cardiol 2006;48:566-75.
7. Henzlova MJ, Duvall WL, Einstein AJ, Travin MI, Verberne HJ. ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers. J Nucl Cardiol 2016;23:606-39.
8. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonell M, *et al.* Development and evaluation of the Seattle Angina Questionnaire: A new functional status measure for coronary artery disease. J Am Coll Cardiol 1995;25:333-41.
9. Morrow DA, Boden WE. Stable ischemic heart disease. In: Mann DL, Zipes DP, Libby P, Bonow RO, editors. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed. Philadelphia: Saunders; 2015. p. 1196-9.
10. Edwards IR, Aronson JK. Adverse drug reactions: Definitions, diagnosis, and management. Lancet 2000;356:1255-9.

11. Tripathi KD. Adverse drug effects. Essentials of Medical Pharmacology. 7th ed. New Delhi: Jaypee Brothers Medical Publishers; 2013. p. 82-3.
12. Wijeysundera HC, Nallamothu BK, Krumholz HM, Tu JV, Ko DT. Meta-analysis: Effects of percutaneous coronary intervention versus medical therapy on angina relief. Ann Intern Med 2010;152:370-9.
13. Sedlis SP, Hartigan PM, Teo KK, Maron DJ, Spertus JA, Mancini GB, *et al.* Effect of PCI on long-term survival in patients with stable ischemic heart disease. N Engl J Med 2015; 373:1937-46.
14. Cairns JA. Ranolazine: Augmenting the antianginal armamentarium. J Am Coll Cardiol 2006; 48:576-8.
15. Chaitman BR, Skettino SL, Parker JO, Hanley P, Meluzin J, Kuch J, *et al.* Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J Am Coll Cardiol 2004;43:1375-82.

Proforma of Anginal Questionnaire:

Name:_____ OP/IP number:_____

Age/sex:_____

Diagnosis:_____

1. The following is a list of activities that people often do during the week.

Activity	Severely limited	Moderately limited	Somewhat limited	A little limited	Not limited	Limited, or did not do for other reasons
Dressing yourself						
Walking indoors on level ground						
Showering						
Climbing a hill or a flight of stairs without stopping						
Gardening, vacuuming, or carrying groceries						
Walking more than a block at a brisk pace						
Lifting or moving heavy objects						

2. Compared with 4 weeks ago, how often do you have chest pain, chest tightness, angina when doing your most strenuous level of activity?

I have had chest pain, chest tightness, or angina.

Much more often	Slightly more often	About the same	Slightly less often	Much less often

3. Over the past 4 weeks, on average, how many times have you had chest pain, chest tightness, or angina?

I get chest pain, chest tightness.

4 or more times/day	1-3 times/ day	3 or more times/week but not every day	1-2 times/ week	<1/ week	None over the past 4 weeks

4. Over the past 4 weeks, on average, how many times have you had to take nitros (nitroglycerin tablets) for your chest pain, chest tightness, or angina?

I take nitros.

4 or more times/day	1-3 times/ day	3 or more times/week but not every day	1-2 times/ week	<1/ week	None over the past 4 weeks

5. How bothersome is it for you to take your pills for chest pain, chest tightness, or angina as prescribed?

Very bothersome	Moderately bothersome	Somewhat bothersome	A little bothersome	Not bothersome at all	My doctor has not prescribed pills

6. How satisfied are you that everything possible is being done to treat your chest pain, chest tightness, or angina?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Highly satisfied

7. How satisfied are you with the explanations your doctor has given you about your chest pain, chest tightness, or angina?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Highly satisfied

8. Overall, how satisfied tie you with the current treatment of your chest pain, chest tightness, or angina?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Highly satisfied

9. Over the past 4 weeks, how much has your chest pain, chest tightness, or angina interfered with your enjoyment of life?

It has severely limited my enjoyment of life	It has moderately limited my enjoyment of life	It has slightly limited my enjoyment of life	It has barely limited my enjoyment of life	It has not limited my enjoyment of life

10. How often do you worry that you may have a heart attack or die suddenly?

I cannot stop worrying about it	I often think or worry about it	I occasionally worry about it	I rarely think or worry about it	I never think or worry about it