ORIGINAL ARTICLE

COMPARISON OF EFFICACY AND SAFETY OF RANOLAZINE AND IVABRADINE IN CHRONIC ISCHEMIC HEART DISEASE PATIENTS

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Background: Ischemic Heart Disease (IHD) frequently produces persistent angina that may significantly impair quality of life despite standard treatment. There is need for effective adjunctive therapies to manage refractory angina. Ranolazine and Ivabradine are two potential 005Coptions that have shown efficacy in alleviating angina symptoms and improving quality of life in IHD patients. **Methods:** Ethical clearance was obtained from hospital ethical committee before initiation of study. Those patients fulfilling study inclusion criteria were enrolled. Written informed consent was obtained from all the patients. This randomized clinical trial enrolled patients from the Department of Cardiology, PIMS Hospital, Islamabad. The information regarding demographic and baseline patient characteristics were recorded. Patients were randomly assigned into two groups by lottery method. Treatment group (Group-A) was Ranolazine 500 mg tablets twice daily for 8 weeks plus standard treatment while the placebo group (Group-B) was Ivabradine 5 mg tablets twice daily for 8 weeks plus standard treatment. The primary outcome of study was improvement in angina as assessed by SAQ. Other outcomes like hemodynamic stability (heart rate and Blood pressure) and associated side effects were also recorded at 2, 4, 6, and 8 weeks after the start of treatment in both the study groups. The collected data was analyzed by using SPSS 23 version. **Results:** The mean age of patients in Group-A was 64.59±5.47 years and in Group-B were 65.41±5.95 years. In Group-A 36(78.3%) patients were male and 10(21.7%) patients were female and in Group-B 38(82.6%) patients were male and 8(17.4%) patients were female. The baseline score of SAQ in Group-A and Group-B was as (41.93±4.23 vs 43.24±4.44) and at 8 week as (90.98±3.12 vs 81.48±2.52). Ranolazine had better clinical outcome than Ivabradine for the treatment of persistent angina in patients with chronic stable ischemic heart disease in terms of SAQ score, systolic & diastolic blood pressure and safety profile. **Conclusion:** This study concluded that Ranolazine in comparison to Ivabradine has better clinical outcomes in terms of efficacy & safety in patients with chronic IHD who had persistent symptoms.

Keywords: Efficacy; Ivabradine; Ischemic heart disease; Ranolazine; side effects

Citation: Niazi AWK, Nisar A, Pirzada SN, Yaqoob N, Naeem M, Malik HS, Bacha MF. Comparison of efficacy and safety of ranolazine and ivabradine in chronic ischemic heart disease patients. J Ayub Med Coll Abbottabad 2024;36(4 Suppl 1):986–90.

DOI: 10.55519/JAMC-S4-14005

INTRODUCTION

Chronic stable ischemic heart disease (IHD) is still a major global health issue, frequently appearing as angina pectoris.[1] Despite the advancements in therapeutic techniques, a significant percentage of individuals continue to endure persistent angina while on appropriate medical therapy.[2] Persistent angina not only reduces quality of life, but it also places a significant burden on healthcare systems.[3] In this context, second-line anti-anginal drugs such as Ranolazine and Ivabradine have received interest due to their distinct modes of action and possible benefits in patients who remain symptomatic despite standard treatment.[4–6] According to the report, by 2030, the projected prevalence rate of ischemic heart disease is expected to surpass the current rate of 1,655 per 100,000 individuals and reach 1,845.[7] In Pakistan the prevalence of IHD was 26.9% in men and 30.0% in women.[8] Ranolazine is a piperazine derivative that acts primarily by inhibiting the late sodium current which reduces intracellular calcium overload, and so improves myocardial relaxation.[9] Ivabradine, on the other hand, selectively suppresses the current in the sinoatrial node result in heart rate reduction without influencing myocardial contractility or coronary vasodilation.[10] Both medicines present potential options for the management of chronic stable angina but their comparative efficacy and safety profiles in this specific patient population remain inadequately explored. The systematic review and meta-analysis revealed that Ivabradine significantly reduced angina episodes and enhanced quality of life in patients with chronic stable angina.[11] A comprehensive

analysis indicated that people with chronic stable ischemic heart disease who experience persistent angina while receiving appropriate pharmaceutical therapy can benefit from using ranolazine and ivabradine as second-line medications.[12]

Another study underlined the function Ranolazine plays in relieving chronic stable angina symptoms, especially in patients not responding to conventional treatments. The results showed that Ranolazine effectively reduced the number of angina episodes and improved exercise performance without significantly affecting heart rate or blood pressure.[13]

The best way to treat persistent angina in people with chronic stable ischaemic heart disease is still a challenge, even with the abundance of therapeutic choices. With their unique modes of action, Ivabradine and ranolazine are useful additions to the treatment toolbox. Nevertheless, not enough research has been done to compare their relative safety and efficacy.

This study aims to compare the efficacy and safety profiles of Ranolazine and Ivabradine in patients with chronic stable IHD who continue to experience angina despite optimal medical treatment. By elucidating the relative benefits and risks of these agents, this research seeks to provide a clearer understanding of their roles in contemporary clinical practice, potentially guiding therapeutic decisions in the management of persistent angina.

MATERIAL AND METHODS

This randomized clinical trial was conducted in the Department of Cardiology at Pakistan Institute of Medical Sciences (PIMS), Islamabad, over a six-month period following the approval of the ethical review committee. The sample size was calculated using the WHO sample size calculator with a significance level of 5%, a power of 80%, a population standard deviation of 0.75, and anticipated differences in the mean number of angina attacks per week between the Ivabradine group (0.1) and the Ranolazine group (0.05).[14] The required sample size was determined to be 46 patients per group, totalling 92 patients. Patient selection was carried out using non-probability consecutive sampling.

Inclusion criteria included patients aged 30–80 years of both genders, diagnosed with chronic IHD presenting with stable angina and persistent symptoms despite optimal medical treatment. Exclusion criteria comprised patients with a history of myocardial infarction or cerebrovascular events, those who had been taking Ranolazine or Ivabradine for at least one month before enrolment, patients with blood pressure >170/100 mmHg or systolic BP<100 mmHg, and individuals with a history of rheumatoid arthritis, renal or hepatic impairment, decompensated heart failure, second-or third-degree heart block, bradycardia, arrhythmias, anemia (Hb<7 g/dL), as well as pregnant or lactating females.

Ethical approval was obtained from the ethical committee of PIMS before the commencement of study. Eligible patients were enrolled from the Cardiology Department at PIMS, Islamabad, and written informed consent was obtained from all participants. Demographic and clinical characteristics of the enrolled patients were recorded. Patients were randomized into two groups using a lottery method. The treatment group (Group-A) received Ranolazine 500 mg tablets twice daily for 8 weeks in addition to standard treatment, while the placebo group (Group-B) received Ivabradine 5 mg tablets twice daily for 8 weeks in addition to standard treatment. It was a single blind study with researcher comparing the effects of both drugs at regular intervals. The patients continued their pre-existing anti-anginal or other medications in addition to the study drug throughout the study. The primary outcome was the improvement in angina, assessed using the Seattle Angina Questionnaire (SAQ) at baseline and at 2nd, 4th, 6th, and 8th weeks after starting treatment. Secondary outcomes included hemodynamic stability, measured by changes in heart rate and blood pressure, and the incidence of associated side effects which were recorded at the same follow-up intervals. All collected data were recorded on a *Proforma*.

Data were entered and analyzed using SPSS software version 23. Continuous numerical variables, such as age, SAQ score, heart rate, and blood pressure, were analyzed as mean±standard deviation (SD). Categorical variables, including gender, baseline comorbidities, and associated side effects, were presented as frequencies and percentages for both groups. The mean difference in SAQ scores from baseline to each follow-up visit (2,4,6, and 8 weeks) was determined using paired sample t-tests within each group. Independent sample *t*-tests were applied to compare SAQ scores between the two groups at each follow-up interval. Differences in the rate of side effects between the two groups at each follow-up visit were analyzed using chi-square tests. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

At baseline, SAQ scores were similar between both groups. However, Group-A (Ranolazine) consistently showed significantly higher scores at 2,4,6, and 8 weeks compared to Group-B (Ivabradine), with the differences being statistically significant at each follow-up point presented in Table-1.

The result in Table-2 depicted that at baseline, heart rates were similar between the groups, with Group-A (Ranolazine) at 74.20±3.50 bpm and Group-B (Ivabradine) at 74.56±4.10 bpm. Throughout the follow-

up periods (2,4,6 and 8 weeks), Group-A's heart rates remained slightly higher than Group-B's, but the differences were not statistically significant at any time point.

Table-3 presented that in the Ranolazine group (Group-A), systolic blood pressure decreased from 132.30±1.56 mmHg at baseline to 122.80±1.47 mmHg at 8 weeks, while diastolic blood pressure decreased from 87.87±1.61 mmHg to 77.02±1.50 mmHg. In the Ivabradine group (Group-B), systolic blood pressure decreased from 132.63±1.78 mmHg at baseline to 126.57±0.50 mmHg at 8 weeks, and diastolic blood pressure decreased from 87.52±1.70 mmHg to 81.00±0.84 mmHg. These findings show that both Ranolazine and Ivabradine were effective at lowering blood pressure throughout the investigation, with the Ranolazine group experiencing slightly higher reductions. shown in Table-4, Ranolazine Group-A patients generally experienced fewer side effects with more than half of patients experiencing no notable side effects. However, dizziness, nausea, and muscle pain were the most common side effects in both groups. Notably, nausea, dizziness & body aches were more frequent in the Ivabradine group throughout the study.

Table-1: Results of SAQ Score in study groups

SAQ Score	Group-A	Group-B	*p*-value
Baseline	41.93±4.23	43.24±4.44	0.152
2nd week	57.35±4.29	51.37±3.91	0.000
4th week	71.76±3.44	62.07±1.47	0.000
6th week	81.20±2.56	70.50±3.58	0.000
8th week	90.98±3.12	81.48±2.52	0.000
8th week	72.10±5.40	69.85±6.40	0.072

Table-2: Results of Heart Rate Score in study groups

Heart Rate	Group-A	Group-B	*p*-value
Baseline	74.20±3.50	74.56±4.10	0.651
2nd week	74.12±3.60	73.10±4.20	0.214
4th week	73.00±4.20	71.00±5.50	0.05
6th week	72.05±5.30	70.10±6.50	0.128

Table-3. Results of blood Pressure (mmHg) in study groups

	Variables	Group-A (Ranolazine)		Group-B (Ivabradine)		*p*-value
		Mean	SD	Mean	SD	
Baseline	Systolic Blood Pressure	132.30	1.56	132.63	1.78	0.353
	Diastolic Blood Pressure	87.87	1.61	87.52	1.70	0.316
At 2nd week	Systolic Blood Pressure	129.52	1.01	132.00	0.82	0.000
	Diastolic Blood Pressure	86.02	1.45	87.09	0.86	0.000
At 4th week	Systolic Blood Pressure	126.98	0.88	129.52	0.51	0.000
	Diastolic Blood Pressure	81.70	1.62	84.87	0.81	0.000
At 6th week	Systolic Blood Pressure	125.07	0.88	128.13	0.88	0.000
	Diastolic Blood Pressure	78.91	0.84	83.00	0.87	0.000
At 8 week	Systolic Blood Pressure	122.80	1.47	126.57	0.50	0.000
	Diastolic Blood Pressure	77.02	1.50	81.00	0.84	0.000

Table-4. Outcome in terms of side effects in study groups

Week	Side effects	Groups		
		Group-A (Ranolazine)	Group-B (Ivabradine)	*p* Value
2nd week	None	19(41.3%)	8(17.4%)	0.590
	Dizziness	4(8.7%)	5(10.9%)	0.439
	Nausea	5(10.9%)	6(13.0%)	0.526
	Vomiting	2(4.3%)	3(6.5%)	0.390
	Vertigo	2(4.3%)	3(6.5%)	0.390
	Backache	3(6.5%)	5(10.9%)	0.217
	Muscle pain	4(8.7%)	6(13.0%)	0.789
	Joint pain	2(4.3%)	3(6.5%)	0.390
	Others	5(10.9%)	7(15.2%)	0.876
8th week	None	25(54.3%)	4(8.7%)	0.010
	Dizziness	4(8.7%)	6(13.0%)	0.075
	Nausea	6(13.0%)	9(19.6%)	0.095
	Vomiting	2(4.3%)	4(8.7%)	0.325
	Vertigo	0(0.0%)	4(8.7%)	0.025
	Backache	1(2.2%)	5(10.9%)	0.125
	Muscle pain	3(6.5%)	5(10.9%)	0.046
	Joint pain	2(4.3%)	3(6.5%)	0.075
	Others	3(6.5%)	6(13.0%)	0.032

DISCUSSION

We conducted this study and found efficacy in terms of SAQ scores, systolic & diastolic blood pressure and safety profile in terms of side effects. Ranolazine had better clinical outcome (p=0.00) than Ivabradine for the treatment of persistent angina in patients with chronic stable ischemic heart disease on optimal medical treatment.

The study carried out by Chaturvedi *et al*. found RAN & IVA are both suitable and effective antianginal drugs with significant effect on the frequency decrease in angina attacks but RAN is better than IVA in efficacy and safety measures (p=0.01).[14]

This study results indicated that Ranolazine led to significantly higher SAQ scores at 2,4,6, and 8 weeks compared to Ivabradine. Previous study depicted that scores of domains of SAQ were higher at six weeks as compared to baseline.[15] Ranolazine may be associated with improvements in CFR and some of the SAQ domains, including angina stability, physical functioning, and quality of life.[16] Both the SAQ score and the EuroQoL VAS improved significantly (p<0.01) in the ivabradine and ranolazine groups from baseline to FU after 4 weeks. Overall, ranolazine showed better results for different SAQ and EuroQoL VAS levels than ivabradine (p<0.05) in this very small cohort of patients.[17]

The current study result depicted that throughout the follow-up periods (2,4,6, and 8 weeks), Group-A's heart rates remained slightly higher than Group-B's, but the differences were not statistically significant at any time point. Previous study reported that IVA change the HR significantly during exercise and at rest, during tolerance test of exercise the HR decreased significantly when compared with the placebo (p=0.05) in the patients that received randomly 10,5,or 2.5 mg of IVA twice in a day for 2 weeks in trial of double blind.[18]

With RAN therapy, hemodynamic parameters significantly improved. In RAN group, there was significant change in the diastolic or systolic BP or the HR, showing that taking 500 mg of the RAN twice a day had positive effect on hemodynamic parameters. Our results are little consistent with others, who found that using RAN as an anti-ischemic had no negative effect on HR, blood pressure, or inotropic state.[19]

We found in this study that RAN is superior and better in its side effects than IVA. The patient's number who had side effects higher in IVA group than RAN group (p=0.001). In IVA patients 19.6% had nausea and in RAN group 13.0% had nausea. Chaturvedi *et al*[20] reported most common side effect was nausea in RAN group while dizziness was in IVA group patients. While the dizziness noted in our study was 13.0% in IVA and 8.7% in RAN group.

Although many patients in IVA group complained of the dizziness, this suggests that patients can be dizzy at start of the treatment because imbalance and dizziness are typical issues in elderly.[21]

Chaturvedi *et al*[20] reported the only side effect that was substantially greater in RAN group than in IVA group was the nausea (26.6 percent). It's unclear whether RAN-induced nausea was caused by CTZ activation, vestibular disruption, or GIT dysfunction. Chaitman *et al* and Stone *et al* reported that constipation, asthenia, nausea and dizziness were that main side effects in the use of these two drugs with difference in both the groups and recommend the use of RAN which is effective and safe in the management and treatment of stable angina conditions. [22,23]

CAD is leading cause of death and morbidity in developed nations. Ranolazine provides a favourable therapeutic strategy in patients with the chronic stable angina who are still symptomatic when receiving effective anti-ischemic treatment, or who are intolerant to standard anti-ischemic medicines, according to Rognoni *et al*.[24]

Chronic stable angina is common illness with significant clinical, social, and economic consequences. Vadnais and colleagues also looked at the new therapeutic function of ranolazine in treatment of angina. Ranolazine is a validated antianginal medicine in patients with the symptomatic CHD, according to researchers, and should be used as an initial antianginal agent in individuals with bradycardia or hypotension.[25] While Ndegwa *et al* reported ranolazine's side effects were as headache, constipation, asthenia, nausea, dizziness and concluded in their study that more ranolazine clinical studies are required to prove its long-term safety, appropriate dosage, effectiveness in conjunction with full-dose of beta-blockers without or with CCB "calcium channel blockers", and potential usefulness in treatment of other disorders of cardiovascular diseases.[26]

According to Tamargo *et al*[27] ranolazine provides an alternative treatment strategy in patients with the chronic stable angina due to its unique mechanism of action, and it can be the first option in presence of comorbidities that make typical medications difficult to employ. These findings confirm the results of our study that ranolazine is better than other medicines.

CONCLUSION

This study has determined that Ranolazine is more effective and safer treatment choice compared to Ivabradine for patients suffering from chronic stable IHD and persistent angina. It offers improved

symptom relief and haemodynamic stability. The management of IHD in clinical practice will be significantly impacted by these findings.

AUTHORS' CONTRIBUTION

All the authors contributed equally to this study including going through the literature, formulation of the study, data collection, analysis and interpretation. Final write-up and rectifying.

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Submitted: June 3, 2024	*Revised: November 4, 2024*	*Accepted: November 29, 2024*

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