

Comparison of the efficacy and tolerability of ivabradine and ranolazine in patients of chronic stable angina pectoris

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ABSTRACT

Introduction: To compare the efficacy and tolerability of Ivabradine (IVA) and Ranolazine (RAN) in chronic angina patients. **Materials and Methods:** This was a follow-on, open-label trial conducted in a tertiary care hospital of Uttarakhand. Thirty patients each taking IVA 5 mg twice daily or RAN 500 mg twice daily were distributed to the respective groups. Patients were asked to fill a pretested questionnaire on frequency of anginal attacks and adverse reactions before and 2, 4 and 8 weeks after taking the respective medicines. Their blood pressure, heart rate and routine hematological and biochemical estimations were performed at baseline and after intervention. Results were statistically analyzed using different statistical tests, with $P < 0.05$ considered as significant. **Results:** There was no significant difference in the frequency of anginal attacks per week between the groups. The adverse drug reactions (ADRs) reported in the IVA group were dizziness (30%), headache (16.6%), backache (16.6%), vertigo (13.3%), blurred vision (13.3%), muscle cramps (10%), arthralgia (10%), cough and dyspnea (6.6%), hypersensitivity rash (6.6%), fever (3.3%) and nausea (3.3%). The ADRs in the RAN group were nausea (26.6%), dizziness (23.3%), vomiting (3.3%), constipation (3.3%) and vertigo (3.3%). The blood pressure, heart rate and routine hematological and biochemical evaluations did not show any significant difference in the pre–post values. IVA significantly decreased the resting heart rate after eight weeks of intervention. **Conclusions:** Both antianginal agents appeared equiactive. However, RAN had a better safety and tolerability profile than IVA. Serum sickness-like reaction was an adverse event noticed with IVA, which needs causality establishment.

Key words: Antianginals, dizziness, equiefficacious, nausea, serum sickness-like reaction

INTRODUCTION

It has been anticipated that by 2020, ischemic heart diseases (IHD) will be the leading cause of global disease

burden.^[1] In the last few decades, its incidence has increased in the economically developing countries. The medicines currently used in the management of chronic stable angina pectoris (CSAP) are mainly β blockers, calcium channel blockers (CCBs) and nitrates.^[2] However, these have some side-effects like negative inotropic effect with β blockers and hypotensive effect with CCBs, which could have serious consequences and jeopardize the management of IHD.

New medicines in the management of coronary artery disease (CAD) include metabolic modulator ranolazine (RAN) and sinus node inhibitor ivabradine (IVA). The antianginal action of RAN is due to blockade of the β oxidation of fatty

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acids and shifting the heart's metabolism to produce more energy as ATP from glucose. Because glucose needs less oxygen to generate the same amount of energy as fatty acids, this can be advantageous in the presence of IHD.^[3] IVA is a specific heart rate (HR) decreasing agent acting on the sino-atrial node by selectively inhibiting the pacemaker I_f current in a dose-dependent manner and reducing HR at rest as well as during exercise with minimal effect on myocardial contractility, blood pressure (BP) and intra-cardiac conduction.^[4,5]

Our literature search did not reveal any trials comparing the tolerability and clinical efficacy of RAN and IVA. Hence, this trial was planned to compare the efficacy and tolerability of the two agents in CSAP patients. Additionally, cost-effectiveness of the two medicines was also studied.

MATERIALS AND METHODS

This was a follow-on, open-label, non crossover trial conducted from May 2010 to July 2010 in a tertiary care hospital of Uttarakhand, with permission from the institutional ethics committee, as a project under short-term studentship (STS) from the Indian Council of Medical Research (ICMR). Patients of either gender, >18 years and < 60 years of age, diagnosed to be suffering from CSAP, attending the cardiology outpatient department of the hospital, taking IVA or RAN for at least 1 month prior to the enrolment in the trial, were approached and requested to participate in the trial. Those who showed interest in joining and fulfilled the inclusion criteria were supplied with a detailed information sheet and briefed about the possible ADRs with the trial medicines in vernacular language and all their questions concerning the trial were answered. Patients with BP > 170/100 mm, systolic BP < 100 mm, history of chronic diabetes mellitus, rheumatoid arthritis, renal or hepatic impairment, pregnancy, lactation, past history of myocardial infarction, cerebrovascular event, severe bradycardia, moderate to severe heart failure, severe hypotension, second- to third-degree heart block, arrhythmias or anemia (Hb < 7 g/dL) were excluded. From those who agreed to participate, informed, witnessed and written consent was taken. One hundred and twelve patients were assessed for eligibility, 45 were excluded, six refused to participate and one was lost to follow-up in the IVA group [Figure 1]. After seeking review and permission from the attending cardiologist, the 30 patients who were started on IVA 5 mg twice daily (M/s Lupin Laboratories Ltd., Mumbai, India) and an equal number taking RAN 500 mg (M/s Cipla Ltd., Mumbai, India) twice daily were included. Trial medicines of the same batch and date of manufacture from the same manufacturer were procured from the local market and supplied free of cost to the participants during the trial period. Patients were monitored on a weekly basis along with ECG recordings.

Dosage of the trial medicines was based on previous studies.^[6,7] Along with the trial medicines, patients were allowed to continue

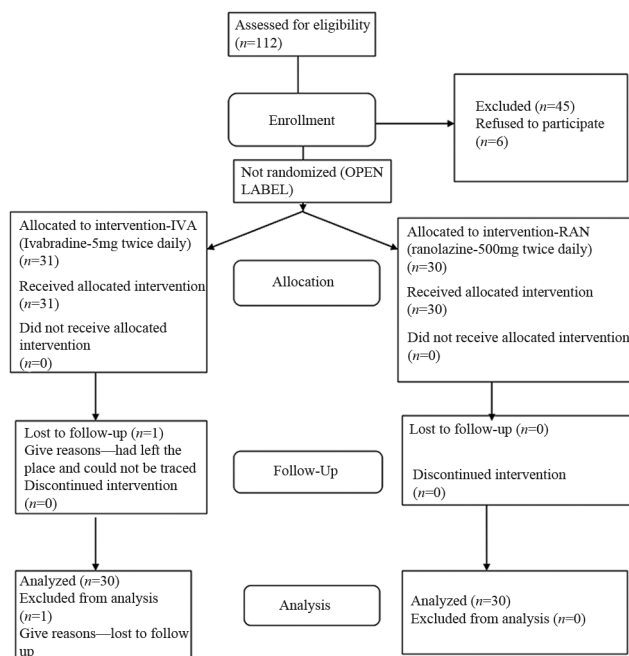


Figure 1: Consort flow chart of the efficacy and tolerability of Ivabradine and Ranolazine in patients of chronic stable angina pectoris

with other antiplatelet, statin, antihypertensive and antianginal therapy on which they were already stabilized. Patients taking CYP3A4 inducers and inhibitors, diltiazem, verapamil, medicines that prolong QT interval (quinidine, disopyramide, sotalol, amiodarone), rifampicin, barbiturates, phenytoin, tricyclic antidepressants, antipsychotics, mefloquine, β blockers, digoxin, simvastatin, paroxetine and cyclosporine were excluded due to known drug interactions with the trial medicines. The antianginal efficacy of the trial medicines (primary outcome) and their ADR profile (secondary outcome) was assessed through a pretested questionnaire in both the groups at baseline and after 2, 4 and 8 weeks of intervention. Patient data was collected by a student investigator who was trained by the supervisor. The questions were related to the frequency of anginal attacks, frequency and duration of ADRs after taking the medicine and treatment taken for the ADRs. Medicine expenditure per month was also calculated. BP, HR, routine hematological (Hb%, serum electrolytes) and biochemical evaluations (LFTs, RFTs, RBS) were done pre- and post intervention. Chi-square test was used to analyze the difference in the frequency of ADRs. Comparison of the frequency of anginal attacks was analyzed using the unpaired “*t*” test. The pre–post comparison of the trial medicines was tested for significance by the paired “*t*” test, with level of significance being < 0.05.

RESULTS

Demographic profile and clinical characteristics

Table 1 compares the demographic profile and clinical characteristics of the patients in the two groups. Patients

included in the trial were farmers (50%, 25%), retired personal (15%, 10%), business men (20%, 20%), teachers (10%, 25%) and housewives (5%, 25%) in the IVA and RAN group, respectively. There was no significant difference (using the unpaired “*t*” test) between the mean age of the patients and the frequency of anginal attacks in the two groups [Table 1].

Investigations of patients at baseline and 8 weeks of treatment

Table 2 shows that Hb, LFTs, RFTs, serum electrolytes and RBS done at baseline and after 8 weeks of use of the IVA and RAN did not show any significant difference (using the paired “*t*” test).

Assessment of antianginal efficacy

There was a highly significant difference ($P < 0.01$) in the frequency of angina attacks at 2, 4 and 8 weeks of treatment with both IVA and RAN when compared with baseline. There was no significant difference in the mean \pm SE of frequency

of anginal attacks/week in the IVA and RAN group at 0, 2, 4 and 8 weeks [Table 3]. Two of 30 patients in the IVA group complained of one anginal attack per week, whereas none from the RAN group complained of such problem at the end of 8 weeks.

Assessment of the adverse drug reactions

Assessment of ADRs reported in the two groups was done at 0, 2, 4 and 8 weeks. Twenty-one of 30 patients from the IVA group and 10 of 30 patients from the RAN group reported ADR at some point of the trial. There was a statistically significant difference ($P < 0.01$) in the number of patients reporting ADR from the IVA and RAN groups. In the IVA group, the most common ADR was dizziness in 30% of the patients at 2, 4 and 8 weeks of trial [other ADRs have been listed in Table 4]. There were occasional reports of hypersensitivity rash (6.6%), fever (3.3%) and nausea (3.3%) throughout the trial period in the IVA group [Table 4]. The most common ADRs in the RAN group were nausea (26.6%) and dizziness (23.3%) in patients at 8 weeks of trial, and the other ADRs have been listed in Table 4. There was a statistically significant difference in the IVA and RAN group for the reporting of nausea at 4 and 8 weeks ($P < 0.05$), headache at 2, 4 and 8 weeks ($P < 0.05$), backache at 2, 4 and 8 weeks ($P < 0.05$), muscle cramps at 2 and 8 weeks ($P < 0.01$) and arthralgia at 2, 4 and 8 weeks ($P < 0.05$). Nausea was significantly more common in the RAN group, whereas headache, backache, vertigo, blurred vision, muscle cramps and arthralgia were more common in the IVA group [Table 4].

Comparison of hemodynamic parameters and cost-effectiveness

Statistically, there was no significant difference in systolic BP, diastolic BP and HR in the RAN group at 0 and 8 weeks of trial [Table 5], whereas IVA significantly decreased the resting HR but did not have a significant effect on the systolic and diastolic BP [Table 5]. The monthly treatment with IVA cost INR 699.3, whereas with RAN it was INR 408.

Table 1: Baseline profile and clinical characteristics of patients in the trial groups

<i>n</i> =30 in each group	Ivabradine (5 mg twice daily)	Ranolazine (500 mg twice daily)
Mean age \pm SEM	60.7 \pm 1.54	59.9 \pm 3.56
Men (%)	95	80
Women (%)	5	20
Mean number of anginal attacks per week \pm SD	1.55 \pm 0.211	1.8 \pm 0.2
Chief complaints (all in numbers)		
Number of patients with chest pain on exertion	28	30
Number of patients with palpitations	8	9
Number of patients with dizziness and weakness	8	5
Number of patients with sweating	2	0
Number of patients with dyspnea	2	2

Table 2: Investigations of patients at baseline and 8 weeks of drug treatment (mean \pm SEM)

Investigations	Ivabradine (<i>n</i> =30) (5 mg twice daily)		Ranolazine (<i>n</i> =30) (500 mg twice daily)	
	Baseline	8 weeks of treatment	Baseline	8 weeks of treatment
Hb (gm%)	12.76 \pm 0.43	12.78 \pm 0.44	13.11 \pm 0.3	13.3 \pm 0.26
Liver function tests				
AST (IU)	39.1 \pm 3.08	40.1 \pm 2.76	36.8 \pm 1.94	37.45 \pm 1.95
ALT (IU)	40.3 \pm 3.4	38.4 \pm 3.11	20.8 \pm 1.97	21.5 \pm 1.86
Serum electrolytes				
Na ⁺ mmol/L	135.3 \pm 1.28	132.1 \pm 2.08	137.4 \pm 1.31	135.5 \pm 2.98
K ⁺ mmol/L	4.07 \pm 0.173	4.09 \pm 0.171	3.97 \pm 0.102	4.24 \pm 0.21
Kidney function test				
BUN mg/dL	20.25 \pm 1.57	23.25 \pm 1.38	17.45 \pm 0.93	19.25 \pm 1.47
Serum creatinine (mg%)	1.035 \pm 0.03	0.99 \pm 0.04	1.02 \pm 0.05	1 \pm 0.03
RBS (mg%)	116.9 \pm 3.33	113.2 \pm 3.49	103.85 \pm 3.36	108.95 \pm 3.57

AST=Aspartate aminotransferase, ALT=Alanine aminotransferase, IU=International unit

DISCUSSION

No trial has so far been reported comparing these two medicines; hence, we lack the data for comparison. Our results show that both IVA and RAN are effective antianginal agents and have a statistically significant effect on reduction of the frequency of anginal attacks ($P < 0.01$). However, RAN was better tolerated than IVA. Both the drugs were equiefficacious at 2 months of trial period as there was no statistically significant difference in the decrease in the frequency of anginal attacks. Two of 30 patients from the IVA group complained of one anginal attack per week, but there was no such complaint in the RAN group. Statistically, there was no significant difference in the laboratory investigations performed at baseline and after 8 weeks of intervention, indicating the safety of both medicines. Contradictory to our findings, there is a report of raised uric acid levels, serum creatinine and eosinophils with IVA.^[8] Hemodynamic parameters were stable with RAN treatment. There was no significant change in systolic and diastolic BP and HR in the RAN group, indicating that 500 mg of RAN twice daily does not alter the hemodynamic parameters. Our results are in agreement with the findings of others, where use of RAN as an anti-ischemic did not affect HR, BP or

inotropic state.^[9,10] IVA significantly reduced the HR, which is in agreement with the report that HR at rest and during peak exercise, during the exercise tolerance test, was significantly decreased when compared with placebo ($P < 0.05$) in patients randomly assigned to receive 2.5, 5 or 10 mg twice-daily doses of IVA for 2 weeks in a placebo-controlled double-blind trial.^[7]

We found RAN to be superior to IVA in its ADR profile. The number of patients who reported ADRs was significantly higher ($P < 0.05$) in the IVA (21/30) group as compared with the RAN (10/30) group. The most frequent ADRs reported by the patients of the RAN group was nausea, whereas dizziness was the most frequent ADR reported by the patients of the IVA group. Although more patients from the IVA group complained of dizziness, it had no statistical significance when the two groups were compared or when the baseline values were compared with post-intervention [Table 1], indicating that patients may be having dizziness at the start of treatment as dizziness and imbalance are common problems in elderly patients.^[11] Nausea (26.6%) was the only ADR that was significantly higher in the RAN group as compared with the IVA group. Whether nausea by RAN was due to CTZ stimulation, vestibular disturbance or GIT dysfunction needs investigation. Others have reported dizziness, nausea, asthenia and constipation as being the frequent ADRs with RAN.^[6] Yet another trial has reported that there was no significant safety concern with RAN, which reiterates our understanding that RAN is safer for use.^[12] 16.6% of the patients in the IVA group and none from the RAN group reported headache after 8 weeks. Headache may have been due to blurred vision, phosphenes, inflammatory mediators, dizziness, bradycardia and postural hypotension. As IVA does not cross the blood-brain barrier, headache could not have occurred due to direct action of IVA on the brain.^[13] The reasoning is hypothetical

Table 3: Number of angina attacks per week in the Ivabradine and Ranolazine groups at baseline, and post-intervention (mean±SEM)

<i>n</i> =30 patients in each group	Baseline	At 2 weeks	At 4 weeks	At 8 weeks
Ivabradine	1.55±0.211	0.4±0.152**	0.1±0.069**	0.1±0.023**
Ranolazine	1.8±0.2	0.5±0.154**	0.05±0.05**	0**
<i>P</i> value (Ivabradine vs. Ranolazine)	0.395	0.647	0.5	0.154

** $P < 0.01$ when compared with the baseline

Table 4: Percentage distribution of patients reporting adverse drug reactions with the intervention (*n*=30 each)

Duration of treatment Medicine administered/ side-effect	2 weeks		4 weeks		8 weeks	
	Ivabradine 5 mg twice daily (%)	Ranolazine 500 mg twice daily (%)	Ivabradine 5 mg twice daily (%)	Ranolazine 500 mg twice daily (%)	Ivabradine 5 mg twice daily (%)	Ranolazine 500 mg twice daily (%)
Nausea	3.3 (1)	13.3 (4)	3.3 (1)	20 (6)	3.3 (1)	26.6 (8)
Vomiting	-	3.3 (1)	-	3.3 (1)	-	3.3 (1)
Constipation	-	3.3 (1)	-	3.3 (1)	-	3.3 (1)
Headache	13.3 (4)	-	16.6 (5)	-	16.6 (5)	-
Dizziness	30 (9)	16.6 (5)	30 (9)	16.6 (5)	30 (9)	23.3 (7)
Blurred vision	-	-	13.3 (4)	-	13.3 (4)	-
Muscle cramps	10 (3)	-	6.6 (2)	-	10 (3)	-
Arthralgia	10 (3)	-	10 (3)	-	10 (3)	-
Backache	16.6 (5)	-	16.6 (5)	-	16.6 (5)	-
Vertigo	10 (3)	3.3 (1)	13.3 (4)	3.3 (1)	13.3 (4)	3.3 (1)
Hypersensitivity rash	6.6 (2)	-	3.3 (1)	-	3.3 (1)	-
Cough/dyspnea	10 (3)	-	6.6 (2)	-	6.6 (2)	-
Fever	-	-	3.3 (1)	-	3.3 (1)	-

Values in parenthesis indicate the number of patients out of 30

Table 5: Comparison of hemodynamic parameters in the ivabradine and ranolazine groups at baseline and after 8 weeks of treatment

n=30 patients each	Ivabradine		Ranolazine	
	Baseline	After treatment	Baseline	After treatment
Systolic BP (mmHg)	130.95±1.83	132.38±1.38	131.81±1.72	130.67±1.26
Diastolic BP (mmHg)	78.76±1.18	79.05±1.19	77.14±1.07	78.38±0.98
Heart rate (per minute)	72.47±0.96	68.28±1.12**	73.14±0.90	73.52±1.05

**P<0.01 using the paired "t" test

and needs further investigation. Phosphenes are luminous phenomena, described as a transient enhanced brightness in a limited area of the visual field. It has been hypothesized that IVA interacts with the visual system by inhibiting hyperpolarization-activated current in retinal cells (I_h).^[14] Thirteen percent of the patients from our trial complained of blurred vision. Others have reported that IVA can interact with the retinal current I_h , which participates in the temporal resolution of the visual system, by curtailing the retinal response to bright light. However, these ADRs do not affect the patient's ability to carry out normal activities.^[15] Patients reported a constellation of symptoms like arthralgias (16.6%), muscle cramps (10%), rash (6.6%) and fever (3.3%), which could be due to a serum sickness-like reaction (SSLR), which otherwise are specific drug reactions usually reported with cefaclor, amoxicillin, sulfonamides, tetracyclines, ciprofloxacin, NSAIDs, barbiturates, carbamazepine, propranolol, thiouracil and allopurinol, not associated with circulating immune complexes. Laboratory abnormalities include normal or mild decreases in serum C3, C4 and CH50 levels and mild proteinuria. In contrast to true serum sickness, renal and hepatic involvement is rare.^[16] In our trial, whether these symptoms were due to SSLR or due to other reasons needs investigation.

Drug detail summary of IVA (*PROCORALAN*; Servier Laboratories Ltd., Suresens, France) mentions that vertigo and muscle cramps are its uncommon side-effects.^[17] Contrary to SSLR, fever was not commonly reported in our trial, and most patients were normothermic in both the groups, with one patient in the IVA group complaining of fever at 4 and 8 weeks of trial. A case report on amoxicillin indicated absence of fever in SSLR; therefore, IVA could have caused SSLR without hyperthermia.^[18] The adverse event of SSLR with IVA needs causality establishment as the genetic makeup of Indians is different from that of the other continents, with most studies being from other countries. It could be possible that IVA may not be suited for the Indian population. As the number of patients in our trial was less, extrapolation of our data needs a larger sample size to confirm and validate our findings.

CONCLUSION

Both antianginal agents appeared equiactive. RAN had a better safety and tolerability profile than IVA. RAN was more cost-effective than IVA. Nausea was the main ADR associated with RAN. IVA had a significantly higher incidence of headache, arthralgias, backache, blurred vision and muscle cramps. SSLR was the new adverse event noticed by us with IVA, which needs causality establishment.

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