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Research Article

An open-label study to assess the effect of a single dose of Nebivolol and Ivabradine on heart rate and pulse wave velocity in hypertensive patients receiving amlodipine

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ABSTRACT

Background: Increased resting heart rate (HR) has emerged as an independent risk factor in the general population and in patients with hypertension, coronary artery disease, and myocardial infarction. HR is strongly and directly associated with arterial rigidity in hypertensive patients. Nebivolol (N) and Ivabradine (I) were established HR lowering agents. In this study, we have evaluated Nebivolol and Ivabradine on HR and pulse wave velocity in hypertensive patients who were receiving Amlodipine.
Methods: A total of 18 hypertensive patients on Amlodipine participated in our study. Nine received Nebivolol and others received Ivabradine. We measured HR, blood pressures (BPs) and carotid-femoral pulse wave velocity (cf PWV - an index of large artery stiffness) non-invasively at baseline and 2 hrs after administration of single oral dose of 5 mg N and 5 mg of I.
Results: The mean change in HR (−21.7±7.1 vs. −13.89±7.4 beats/min p=0.03) and cf PWV (−0.27±0.58 vs. −2.31±2.1 m/s p=0.01) was statistically significant after treatment in N and I groups respectively. However, there was no significant change in systolic BP (−17.3±9.1 vs. −15.1±11.1 mmHg p=0.65) and diastolic BP (−3.5±5.0 vs. −8.0±6.4 mmHg p=0.11) after treatment in N and I groups, respectively.
Conclusions: Nebivolol is an effective HR lowering agent compared to Ivabradine. However, significant decrease in arterial stiffness was observed with Ivabradine.

Keywords: Nebivolol, Ivabradine, Arterial stiffness, Carotid femoral pulse wave velocity, Amlodipine

INTRODUCTION

The sympathetic nervous system (SNS) plays an important role in the regulation of blood pressure (BP) homeostasis and cardiac function. Elevated sympathetic activity not only plays a role in the induction of ischemia due to reflex tachycardia and coronary vasoconstriction, but also correlates with hypertension, insulin resistance and coronary

risk. Therefore, the increased SNS activity is a predictor of mortality in patients with these cardio-vascular diseases. And the interference of sympathetic activation may reduce cardiovascular risk. Thus, antihypertensive pharmacotherapy and its influence on the SNS are of great importance.

Calcium channel blocker (CCB) reduces the calcium inflow through blockade of slow voltage-dependent L-type calcium channels and lead to peripheral vasodilation and to inhibit the effects of vasoconstrictor hormones at the level of vascular smooth muscle. Amlodipine, a newer, slow-acting dihydropyridine-type CCB, seems to stimulate SNS to a lesser degree than previous dihydropyridines. Nevertheless, heart rate (HR) and plasma norepinephrine increased significantly in hypertensives after acute application, but the long-term effect on HR was not demonstrated yet.

Increased resting HR has emerged as an independent risk factor both in the general population and in patients with hypertension, coronary artery disease, and myocardial infarction.[1-4] In patients with coronary heart disease, increased resting HR may influence the progression of coronary atherosclerosis.[5] The underlying mechanisms are only partially understood and appear to involve alterations of mechanic properties such as reduction of vascular compliance or its inverse, increased arterial stiffness.[6] HR was also shown to be a main determinant of arterial stiffness. Similarly, HR is strongly and directly associated with arterial rigidity in hypertensive patients, after adjustment for age and BP.[7] The other possible explanations from animal studies reveals that accelerated HR is associated with cellular signaling events leading to vascular oxidative stress, endothelial dysfunction, and acceleration of arterial vascular disease.[8,9] Lowering of HR appears to be one of the most important therapeutic approaches in the treatment of cardiovascular morbidity. So far, beta blockers are the commonly used HR lowering agents in the clinical setting. However, beta blockers are limited by its adverse reactions like tolerance and rebound phenomenon on sudden withdrawal and contraindications.[10,11]

Nebivolol, (N) a selective β1-blocker is an HR lowering drug with nitric oxide (NO) donor properties, have shown to improve endothelial function in hypertensive subjects and increased arterial stiffness, plays an important role in the early atherosclerotic process.[3,12] Ivabradine (I) being an If channel blocker, has a pure HR-lowering action that would prevent angina without adverse effects of beta-blockers. Ivabradine reduces myocardial oxygen demand and simultaneously improves oxygen supply. In contrast to Nebivolol, Ivabradine has no negative inotropic or lusitropic effect which preserves ventricular contractility, do not cause rebound phenomenon on withdrawal, no tolerance on prolonged use and does not change any major electrophysiological parameters unrelated to HR.[13] Prospective clinical data are limited, and prospective evidence determining whether modulation of HR can reduce cardiovascular events in different patient population is needed. In this study, we assessed the magnitude of HR lowering effects after administration of a single dose of these two agents and compared the acute effects on hemodynamic and indices of arterial stiffness on hypertensive patients receiving Amlodipine.

METHODS

The study was conducted at Narayana Medical College Hospital, Nellore. The Institutional Ethical Committee approved the study protocol. All the subjects enrolled into the study gave written informed consent for study participation. A total number of 18 hypertensive patients receiving 5 mg Amlodipine with sitting systolic BP (SBP) between 140 and 160 mmHg and diastolic BP (DBP) between 90 and 99 mmHg, participated in the study. Randomization was carried out using Graph pad software generated random numbers. Nine patients received N and remaining nine received I. All the subjects underwent a medical examination. demographic data, personal and medical history, drug usage and drug allergy were recorded. Subjects in the age group between 20 and 60 years were included in the study. Patients were excluded from the study, if they were pregnant or lactating, having renal, hepatic, and cardiac conduction disorders and if they were hypersensitive to N and I. At baseline HR, BP, and carotid-femoral pulse wave velocity (cf PWV - a marker of arterial stiffness) were measured. The test was repeated 2 hrs after oral administration of 5 mg of N and 5 mg of I.

Measurement of pulse wave velocity

The subjects were examined in the supine position after a 10 mins rest on the bed in a temperature controlled room in the cardiology department. The cf PWV was measured using an automated waveform analyzer (Periscope, M/S Genesis Medical Systems, Hyderabad). This instrument records HR from electrocardiogram, BPs by an oscillometric pressure sensor and cf PWV by a plethysmographic sensor. Earlier report has validated the instrument with optimum acceptable range.[14]

Statistical analysis

Data were entered into excel spreadsheet 2007 and analyzed using Graph pad version-4. Continuous data were expressed as mean±standard deviation. Categorical data were expressed as numbers.

With-in group analysis was performed using paired t-test and between-group analyses by unpaired t-test. Categorical variables were analyzed with "Fischer's exact test." All the efficacy parameters were presented as an absolute change from baseline. A negative sign indicates a decrease and *vice versa*. A two-tailed $p<0.05$ was considered statistically significant.

RESULTS

There were 6 males and 3 females in the N group and 8 males and 1 female in I group. There was no statistically significant difference in the demographic parameters like age (37±11 vs. 44.1±12.4 year, p=0.21), height (164.82±18.34 vs. 162.2±12.7 cm, p=0.72); weight (65.48±9.62 vs. 72.1±14.8 kg, p=0.27) and body mass index (24.35±3.54 vs. 27.4±4.6 cm/kg^2, p= 0.13) between N and I group, respectively. Evaluation of the baseline hemodynamic parameters as shown in Table 1, shows that there was no significant difference in HR (89.2±7.4 beats/min vs. 91.8±15.2 beats/min, p=0.65) and SBP (122.8±11.2 mmHg vs. 132.1±13.1 mmHg, p=0.12) DBP (72.5±5.6 mmHg vs. 78.2±8.7 mmHg, p=0.11) in N and I group, respectively. The cf PWV, a marker of arterial stiffness was found to be not statistically significantly between N and I group (8.34±1.49 m/sec vs. 10.22±2.36 m/sec, p=0.06), respectively.

Following 2 hrs of treatment with Nebivolol, we found a significant decrease in HR (89.2±7.4 vs. 67.5±7.14, beats/min, p<0.0001) and SBP (122.8±11.2 vs. 110±9.57 mmHg p=0.02) compared to baseline. On the other hand, DBP (72.5±5.6 vs. 68.8±.32 mmHg p=0.24) and cf PWV (8.34±1.49 vs. 8.07±1.70 mmHg p=0.73) was similar to baseline. Ivabradine significantly decreased HR (91.8±15.2 vs. 77.91±12.41 beats/min, p=0.04) and cf PWV (10.22±2.36 vs. 7.91±2.15 mmHg p=0.04) as compared to baseline. However, such significance was not found in SBP (132.1±13.1 vs. 120.44±16.9 mmHg p=0.12), DBP (78.2±8.7 vs. 73.22±8.1 mmHg p= 0.22) (Table 2).

The mean change (Table 3) in HR (−21.7±7.1 vs. −13.89±7.4 beats/min p=0.03) and cf PWV (−0.27±0.58 vs. −2.31±2.1 m/s p=0.01) was statistically significant after treatment in N and I groups respectively. Conversely, there was no significant mean change in SBP (−17.3±9.1 vs. −15.1±11.1 mmHg p=0.65) and DBP (−3.5±5.0 vs. −8.0±6.4 mmHg p=0.11) in N and I groups, respectively, as shown in Figures 1 and 2.

All the subjects who participated in the study showed good compliance and none of them developed any adverse effects.

Table 1: Comparison on demographic, hemodynamic, and vascular parameters.

Parameters	Nevibolol (5 mg) (n=9)	Ivabradine (5 mg) (n=9)	p value
Gender	Male: 6 Female: 3	Male: 8 Female: 1	0.57
Age (years)	37±11	44.1±12.4	0.21
Height (cm)	164.82±18.34	162.2±12.7	0.72
Weight (kg)	65.48±9.62	72.1±14.8	0.27
Body mass index	24.35±3.54	27.4±4.6	0.13
HR (beats/min)	89.2±7.4	91.8±15.2	0.65
SBP (mmHg)	122.8±11.2	132.1±13.1	0.12
DBP (mmHg)	72.5±5.6	78.2±8.7	0.11
cf PWV (m/s)	8.34±1.49	10.22±2.36	0.06

HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, cf PWV: Carotid femoral pulse wave velocity

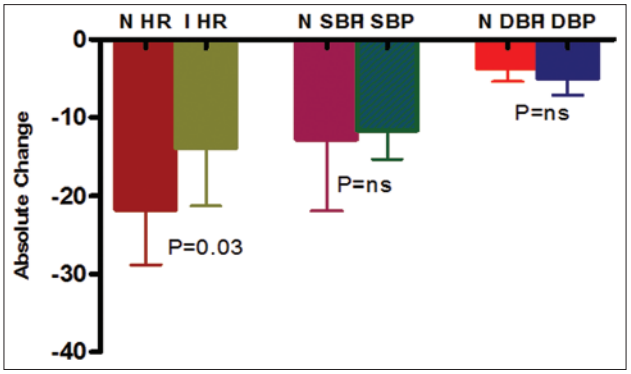

Figure 1: Mean change in hemodynamic parameters after Nebivolol (N) and Ivabradine (I).

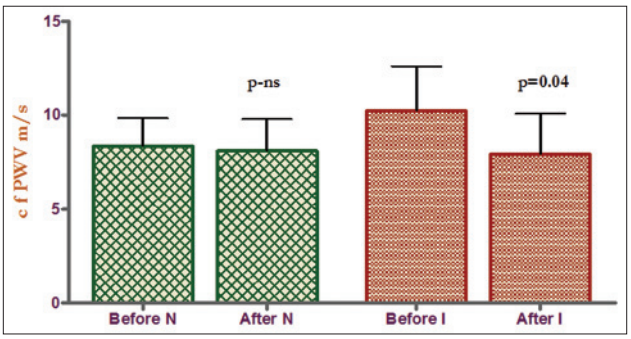

Figure 2: Carotid femoral pulse wave before and after Nebivolol (N) and Ivabradine (I).

Table 2: Comparison of hemodynamic and vascular parameters.

Parameters	Parameters			Parameters		
	Pre	Post	p value	Pre	Post	p value
HR (beats/min)	89.2±7.4	67.5±7.14	<0.0001	91.8±15.2	77.91±12.41	0.04
SBP (mmHg)	122.8±11.2	110±9.57	0.02	132.1±13.1	120.44±16.9	0.12
DBP (mmHg)	72.5±5.6	68.8±7.32	0.24	78.2±8.7	73.22±8.1	0.22
cf PWV (m/s)	8.34±1.49	8.07±1.70	0.73	10.22±2.36	7.91±2.15	0.04

HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, cf PWV: Carotid femoral pulse wave velocity

DISCUSSION

The resting HR is associated with cardiovascular morbidity and mortality in the general population and in patients with cardiovascular diseases. One of the underlying mechanisms involves alterations in HR and vascular compliance or arterial stiffness. Reports have exposed the association between elevated HR and arterial rigidity in normotensives as well as in hypertensive subjects.[15] In a 6 years longitudinal study, Benetos et al.,[16] found that increased HR was one of the important predictors of accelerated progression in pulse-wave velocity. Tomiyama et al.[17] found the association between changes in HR and corresponding alterations in pulse-wave velocity, a marker of arterial stiffness.

Nebivolol, a selective ß1-adrenergic receptor antagonist and Ivabradine is an inhibitor of If current which is an important pacemaker current in the sinoatrial node[18,19] are two HR lowering agents belonging to a different class. Ivabradine, a pure HR-reducing agent, offers the advantage over beta blockers in having no negative inotropic, hypotensive effects, left ventricular systolic and diastolic functions.[20] Additionally, tolerance and rebound has not been reported with Ivabradine at the dosages used. For this reason, we compared beta blocker Nebivolol with Ivabradine on systemic hemodynamics and vascular compliance in hypertensive patients receiving Amlodipine.

When we treated our study participants, we found a significant decrease in HR as compared to the baseline in both N and I groups. N statistically lowered HR than I. However, the differences in the reduction of BPs between N and I groups were not statistically significant. Acute administration of N, Per se, has no significant change large artery stiffness (cf PWV) from the baseline. However, there was a minor change in vascular resistance. This favorable profile on vascular dynamics consistently differentiates Nebivolol from non-vasodilating beta-blockers, where their use may result in increased peripheral vascular resistance after a single dose of therapy due to unopposed alpha-adrenergic activation. Interestingly, Ivabradine significantly decreased cf PWV, a marker of arterial wall stiffness compared to Nebivolol.

One of the probable reasons for our findings may be, firstly, beta-blockers decrease the HR by causing a disproportionate increase in the duration of systole leading to the augmentation of central systolic pressure[21] whereas Ivabradine prolongs diastole and also does not induce adrenergic vasoconstriction.[22] Similarly Colin et al.[23] have shown that the increase in the duration of diastole is greater with Ivabradine than with atenolol for a given HR. These properties will have beneficial effects on the relative timing of reflected pressure waves in the proximal conduit arteries.[22] Thus, an impact of heart-rate reduction (HRR) on the outcome may depend on the means by which HR is lowered. Hence, there was a decrease in augmentation pressure and arterial stiffness by Ivabradine. Second, HRR by If-channel inhibition has recently been shown to increase endothelial nitric oxide synthetase expression, NO availability, restore endothelial function, reduce oxidative stress and atherosclerosis in mouse models of hypercholesterolaemia and endothelial dysfunction.[24,25]

Our study results are supported by conduit artery function evaluation study, the higher central BP with beta blockers, was attributed mainly to a shift of the reflected wave into late systole due to the decrease in ejection duration at lower HRs and also to the vasoconstrictor effect of beta blockers on the peripheral circulation which increases pulse-wave reflection as compared with a calcium entry blocker–angiotensin-converting enzyme-inhibitor association in noncardiac patients.[26] In the initiative trial,[27] comparing Ivabradine with atenolol, Ivabradine induced a similar improvement in exercise capacity than atenolol for a comparatively smaller reduction in RPP and HR.

Study limitations

In the present study, we non-invasively measured central artery stiffness by oscillometric technique and peripheral artery tone by digital plethysmography, which records, pressure waves and calculate the velocities from the contour of these recordings. Furthermore, results should be interpreted with caution because of small sample size.

CONCLUSIONS

It is well-known that HRR results in improvement of arterial stiffness. Nebivolol, a potent HR lowering agent compared to if inhibitor Ivabradine did not significantly decrease the arterial stiffness in our single dose study.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee.

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