Research Article

A Comparative clinical study on the Combination Therapy of Nebivolol/Amlodipine with Atenolol/Amlodipin in the management of hypertension

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Abstract

Objective: The primary objective of this study was to demonstrate that nebivolol–amlodipine combination therapy is superior to atenolol-amlodipine combination therapy with respect to mean fall in systolic blood pressure (SBP) and diastolic blood pressure (DBP). The secondary objective was to compare the response rate and to evaluate the tolerability of study medications between two treatment groups. **Materials and methods:** The two treatment groups were similar with respect to demographic characteristics. For data analysis, the whole population was divided into 2 subgroups, escalated patients and non-escalated patients. A total of 190 eligible patients (Nebivolol/Amlodipine combination therapy: 94; Atenolol/Amlodipine: 96) satisfying inclusion/exclusion criteria were enrolled on the study. This study was carried out at **Syncorp Clinicare Technologies private Ltd**, during the period of eight months from Jan 2013 to Aug 2013 in the academic year 2011-2013. **Results and conclusion:** The results of our study confirmed that the combination therapy with Nebivolol /amlodipine is superior to atenolol/Amlodipine combination therapy in patients with mild-to-moderate essential hypertension. In conclusion, our study has shown that once daily treatment with Nebivolol /amlodipine offers superior antihypertensive efficacy over atenolol/Amlodipine combination therapy in patients with mild-to-moderate essential hypertension.

Key words: Nebivolol, amlodipine, atenolol, heart, hypertension

Introduction

High blood pressure with no known cause is called primary (formerly called essential) hypertension. Between 85% and 95% of people with high blood pressure have primary hypertension. Several changes in the heart and blood vessels probably combine to increase blood pressure. For instance, the amount of blood pumped per minute (cardiac output) may be increased, and the resistance to blood flow may be increased because blood vessels are constricted. Blood volume may be increased also. The reasons for such changes are not fully understood but appear to involve an inherited abnormality affecting the constriction of arterioles, which help control blood pressure. Other changes may contribute to increases in blood pressure, including accumulation of excessive amounts of salt inside cells and decreased production of substances that dilate arterioles.

High blood pressure with a known cause is called secondary hypertension. Between 5% and 15% of people with high blood pressure have secondary hypertension. In many of these people, high blood pressure results from a kidney disorder. Many kidney disorders can cause high blood pressure, because the kidneys are important in controlling blood pressure. For example, damage to the kidneys from inflammation or other disorders may impair their ability to remove enough salt and water from the body (Promising, 1994), increasing blood volume and blood pressure. Other kidney disorders that cause high blood pressure include renal artery stenosis (narrowing of the artery supplying one of the kidneys), which may be due to atherosclerosis, injury, or other disorders.

One of the most serious health problems related to untreated high blood pressure, atherosclerosis contributes to coronary artery disease. Learn about symptoms, diagnoses, and

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treatment of atherosclerosis (Vrancken Peeters, 1994). A stroke occurs when blood flow to an area in the brain is cut off and people who have hypertension are four to six times more likely to have a stroke. Stay safe: Learn your risk factors and the warning signs of stroke and what to do in a stroke emergency (Burrows, 1990).

Angiotensin converting enzyme (ACE) inhibitors are medications that widen or dilate your blood vessels to improve the amount of blood your heart pumps and lower blood pressure. ACE inhibitors also increase blood flow, which helps to decrease the amount of work your heart has to do and can help protect your kidneys from the effects of hypertension and diabetes.

ACE inhibitors are used to treat a number of heart-related conditions, including high blood pressure (Hanley, 1993), heart failure, heart attack and preventing kidney damage associated with hypertension and diabetes. Examples of ACE inhibitors include.

Materials and methods

Study Design: This randomized, comparative, multicentre, 12 week, outpatient study evaluated antihypertensive efficacy of nebivolol/amlodipine combination in comparison with atenolol /amlodipine alone. Patients were selected into two groups:

Group I: Fixed Dose Combination of Nebivolol (5mg) plus Amlodipine (2.5mg)

Group II: Fixed Dose Combination of Atenolol (25mg) plus Amlodipine (2.5 mg)

The study drugs were administered orally once daily in morning.

Patient selection

Willing to sign informed consent and ready for regular follow-up we enrolled in the study.

Inclusion criteria

Patients (either untreated or pre-treated with anti-hypertensive agents) of either sex, aged 18 years and above, diagnosed of essential hypertension.

Exclusion criteria

Patients with DBP >109 mmHg were excluded from the study. Patients with secondary hypertension, known history of hypersensitivity to study medication, patients with severe hypertension, significant medical illness, patients with electrolyte imbalance, abnormal hepatic, and renal functions were excluded from the trial.

Pregnant and lactating women or females of childbearing potential not practicing contraception were excluded from the study.

Ethics Committee

The study was approved by independent ethics committee of each centre. All patients were provided an oral explanation about the nature of the study and about study drugs by the investigator at each centre. An information sheet was provided in a language understood by the patient, and written informed consent was obtained from each participant before any study related procedure. The execution and monitoring of the study was done in accordance with the requirement s of good clinical practice.

Efficacy Evaluation

Efficacy of the therapy in treated patients was evaluated by BP measurement a teach study visit throughout study period. Blood pressure was measured by auscultator method. Measurements were performed after 10 minutes rest in duplicate separated by 2 minutes and then average was taken. If the first 2 readings of DBP differed by more than 5 mmHg, additional reading was obtained and average of 2 closest reading was taken. The study investigator at each site performed all the BP measurements throughout the study period. The same method was followed at all study sites for B P measurement. Patients were termed as responder if their BP was controlled (SBP, 140 mmHg and DBP < 90 mmHg).

Safety Evaluation

All enrolled patients were evaluable for tolerability assessment. Safety evaluation was based on adverse events (AEs) reported during the study. AEs were categorized by the investigator based on their intensity as mild, moderate, or severe and the relationship to the study drug as none, probably not, possible, probable or definite. At every visit during the entire study period, the reported AEs, clinical state of patients and details of concomitant medications, if any were captured. Blood samples were obtained at baseline and at the end of 3 months therapy or at last follow-up visit for early termination/withdrawal cases to perform hematology and biochemistry tests including complete blood count urine routine, electrocardiogram, serum electrolytes (Na+2,Cl+,K), fasting blood glucose.

Statistical analysis

The primary objective was to show that nebivolol / amlodipine combination therapy is superior to atenolol/amlodipine combination therapy with respect to mean fall in SBP and DBP at the end of therapy from baseline. The sample size calculation required approximately 192 patients to be randomized and 174 evaluable patients (87 patients per treatment group) to complete the study to detect a treatment difference of at

least 5 mmHg in the primary comparison with a power of 80% at 5% level of significance (2 sided).

Descriptive statistics, including mean, SD, frequency counts and percentage for categorical variables were used to compare treatment groups at baseline with respect to demographic characteristics. The treatment groups were compared for homogeneity at baseline using tests like Student's t test, Mann–Whitney U test for continuous variables and chi-square test or Fisher's exact test for categorical variables.

The 2 treatment groups were similar with respect to demographic characteristics. For data analysis, the whole population was divided into 2 subgroups, escalated patients and non escalated patients. None escalated patients included patients who received the baseline therapy up to 1 month and remained controlled on the same therapy to the end of study. While escalated patients include patients continued on the baseline therapy up to 1 month but escalate d to respective step-up therapies due to poor or no response to the baseline therapies. Both the treatment groups were compared after 1 month and the end of the study using Student's t test, Mann – Whitney U test as appropriate. All statistical tests we resided and the level of significance were set at 0.05. Statistic al analysis was performed using statistical software Graph Pad Prism 6.01.

Results

Patient distribution

A total of 190 eligible patients (Nebivolol/Amlodipine combination therapy: 94; Atenolol/Amlodipine: 96) satisfying inclusion/exclusion criteria were enrolled on the study. Nine patients from combination group and six patients from mono therapy group were lost to follow-up 1 patient from combination group was withdrawn due to adverse event. A total of 174 patients completed the study (Ne/Am combination therapy: 84; At/Am combination therapy: 90). The 2 treatment groups were similar with respect to demography and baseline disease characteristics (Table 1).

Efficacy after 4 weeks of therapy

At the end of 4 weeks of therapy, 62 patients from Ne/Am combination group and 50 patients

from At/Am combination group responded to the therapy (SBP < 140 mmHg and DBP < 90 mmHg) (P = 0.012) (Table 2). Mean fall in SBP (-30 .0 ± 10.4 vs. -25.08 ± 9.05; P = 0.008) and DBP (-18 .10 ± 7.45 vs. -14.78 ± 7.48; P = 0.021) was significantly superior in Ne/Am combination therapy as compared with At/Am combination therapy at the end of 4 weeks. Mean SBP and mean DBP was significantly lower in Ne/Am combination group as compared with At/Am combination therapy group at the end of 4 weeks of therapy (P < 0.05) (Table 2). Responders from both the treatment groups remained controlled till the end of therapy (day 90). Figure 1 show s fall in mean SBP and DBP for responders on starting therapies.

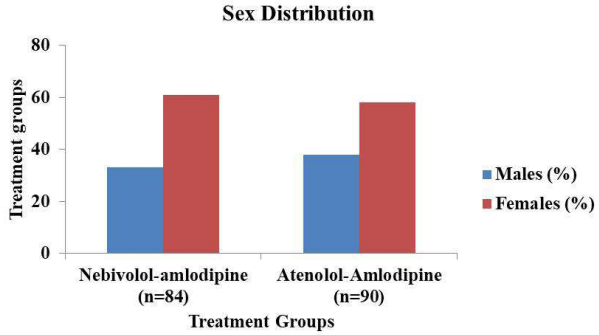

Figure 1. Treatment groups

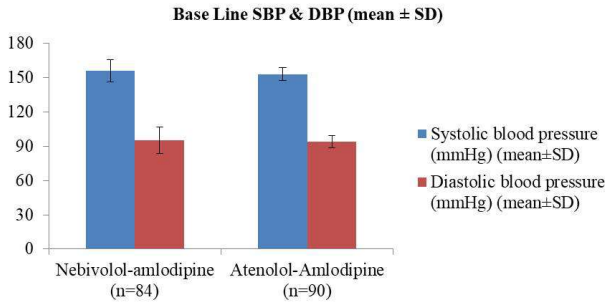

Figure 2. Base Line SBP & DBP

Table 1. Baseline characteristics of patients

Parameters	Nebivolol-amlodipine (n=84)	Atenolol-Amlodipine (n=90)	*P* value
Males (%)	33 (35.11)	38 (39.58)	0.524
Females (%)	61 (64.89)	58 (60.42)	-
Mean age (years) (range)	53.3 ±12.0 (25-80)	55.2±11.9(28-80)	0.274
Mean weight (kg) ±SD	61.1 ±10.8	59.8±10.7	0.395
Mean height (cm) ±SD	158.1 ±10.3	156.9±10.2	0.422
Heart rate (breaths/min) ±SD	79.62 ±7.54	79.46±6.86	0.880
Respiration rate (breaths/min) (mean± SD)	15.50± 2.96	15.49±2.53	0.979
Stage I essential hypertension	53	62	0.248
Stage II essential hypertension	41	34	-
Systolic blood pressure (mmHg) (mean±SD)	156.17 ±9,82	153.1±11.6	0.051
Diastolic blood pressure (mmHg) (mean±SD)	95.06± 5.79	94.07±5.54	0.230

Table 2. Changes in baseline BP measurements for responders at the end of 4 weeks of therapy

Efficacy parameters	Nebivolol-amlodipine(n=62)	Atenolol-Amlodipine (n=50)	*P* value
Mean SBP (mmHg)(at baseline) (mean ±SD)	154.77±9.29	152.68±8.37	0.213
Mean SBP(mmHg)P (at 4 weeks) (mean ±SD)	124.74±6.76	127.60±7.97	0.046
Mean DBP (mmHg) (at baseline) (mean ±SD)	95.35±5.90	94.64±5.02	0.490
Mean DBP (mmHg) (at 4 weeks) (mean ±SD)	77.26±5.59	79.86±5.66	0.017
Mean fall in SBP (mmHg) (mean±SD)	-30.0±10.4	-25.08±9.05	0.008
Mean fall in DBP (mmHg) (mean ±SD)	-18.10±7.45	-14.78±7.48	0.021

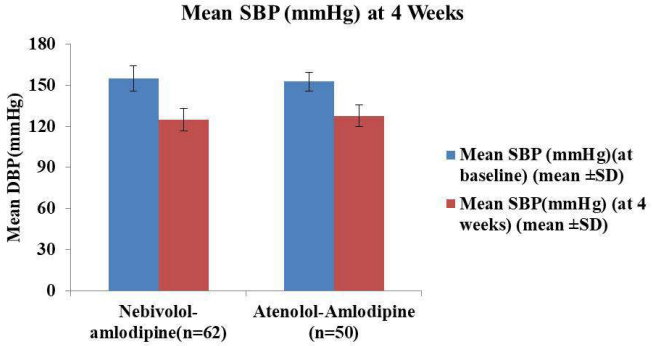

Figure 3. Mean SBP (mmHg) at 4 Weeks

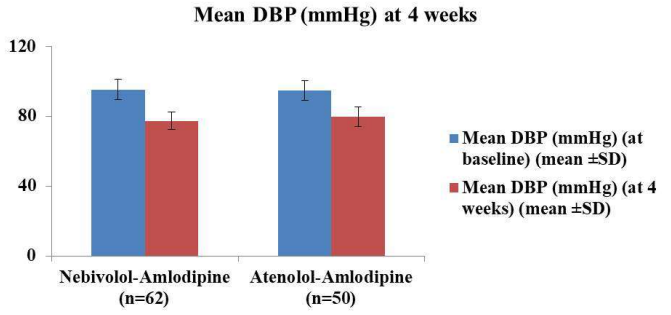

Figure 4. Mean DBP (mmHg) at 4 weeks

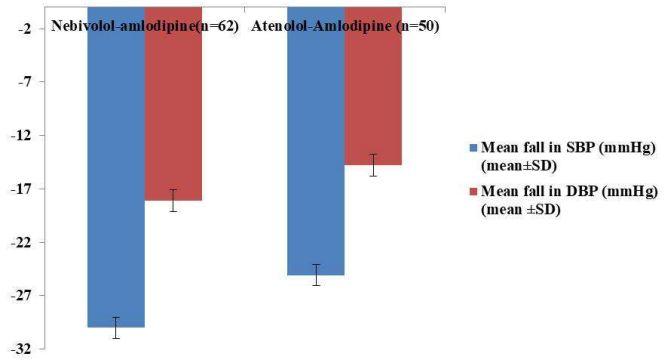

Figure 5. Mean fall in SBP and Mean fall in DBP

Efficacy after 12 weeks of therapy

Sixty-two non responders (Ne/Am combination therapy:22; At/Am combination therapy:40) were escalated to respective step-up therapies to receive Nebivolol 5 mg/ Amlodipine 2.5 mg and atenolol 50 mg/ Amlodipine 2.5 mg for further 8 weeks. At the end of therapy, total 23 patients (Ne/Am combination therapy: 12; At/Am combination therapy group: 11) responded to the step-u p therapies (SBP < 140 mmHg and DBP < 90 mmHg). Step-up therapy of Ne/Am combination group showed significantly better response rate as compared with step-up therapy of atenolol/Amlodipine (P = 0.035) (Table 3).

Both the step-up therapies were comparable with respect to mean fall in SBP and mean fall in DBP (P > 0.05) at the end of therapy. However, at the end of 12 weeks, mean SBP (127.82 ± 8.90 vs. 138.0 ± 14.4; P = 0.001) and mean DBP (81.73 ± 8.78 vs. 87.35 ± 5.50; P = 0.011) were significantly lower in Ne/Am combination group as compared with those in At/Am combination therapy group (Table 3). Nonresponders at the end of treatment period (10: Ne/Am combination group and 29: At/Am combination therapy group) were then treated appropriately at the discretion of the investigator.

At the end of therapy, significantly more number of combination treated patients achieved normalization of BP (SBP < 120 mm Hg and DB P < 80 mmHg) as compared with At/Am combination therapy (33 vs. 19) (P = 0.009). In both the treatment groups, the fall in BP was maximum at the end of 4 weeks of therapy, and subsequently the fall was maintained till the end of therapy, that is, day 90 (Figure 2).

Table 3. Changes in baseline BP measurements for nonresponders at the end of therapy

Efficacy parameters	Nebivolol-amlodipine (n=22)	Atenolol-Amlodipine (n=40)	*P* value
Mean SBP (mmHg) (at 4 weeks)	136.1 ±10.3	142.9 ±10.3	0.016
Mean SBP (mmHg) (at 12 weeks)	127.82 ±8.90	138.0 ±14.4	0.001
Mean DBP (mmHg) (at 4 weeks)	88.36 ±4.60	89.05 ±6.84	0.640
Mean DBP (mmHg) (at 12 weeks)	81.73 ±8.78	87.35 ±5.50	0.011
Mean fall in SBP (mmHg)	-10.1 ±10.4	-4.6 ±6.1	0.109
Mean fall in DBP (mmHg)	-6.64 ±8.74	-2.70 ±6.80	0.076
Responders	12	11	0.035
Nonresponders	10	29	-

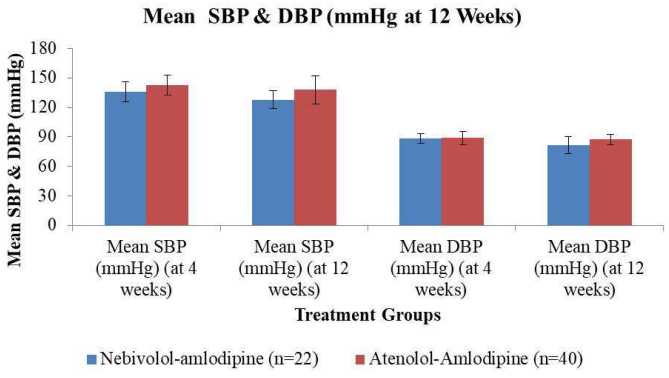

Figure 6. Mean SBP&DBP(mm Hg at 12 weeks)

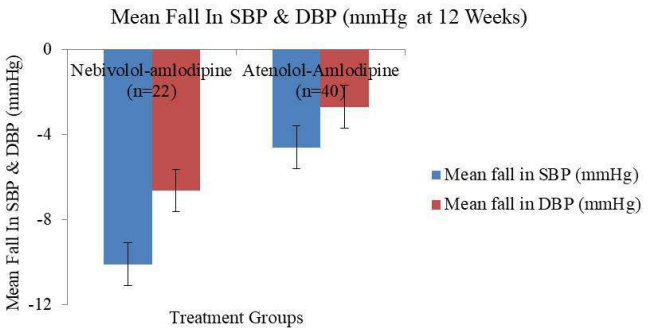

Figure 7. Mean fall in SBP &DBP(mm Hg at 12 Weeks)

Table 4. Mean changes in serum electrolytes and blood sugar from baseline to end of study for all patients

Laboratory parameters	Visit	Nebivolol-amlodipine (n=84)	Atenolol-Amlodipine (n=90)	*P* value
Sodium (mEq/L)	**Baseline**	137.46 ±5.03	137.17 ±4.63	0.619
	End	137.46 ±5.40	137.66 ±5.40	
	***P* value**	1.0	0.441	
Potassium (mEq/L)	**Baseline**	3.99± 0.68	4.03± 0.72	0.600
	End	4.14 ±0.56	4.26 ±0.54	
	***P* value**	0.129	0.025	
Random blood glucose (mg/dL)	**Baseline**	113.93 ±47.54	102.24 ±23.59	0.245
	End	103.66 ±48.99	105.03 ±29.51	
	***P* value**	0.328	0.480	

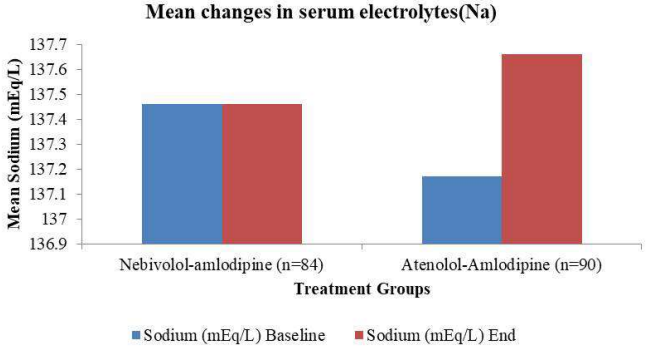

Figure 8. Mean changes in serum electrolytes (Na)

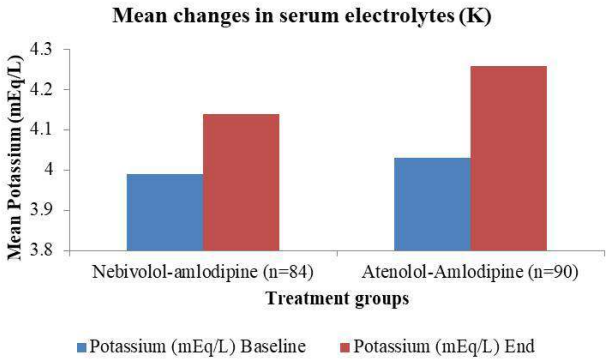

Figure 9. Mean fall in Serum electrolytes (K)

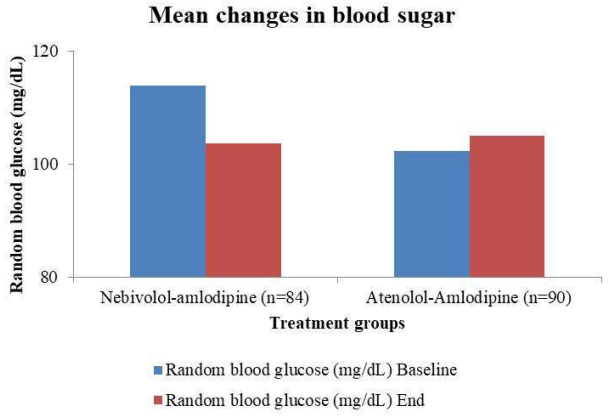

Figure 10. Mean Changes in blood sugar

Tolerability assessment

A total of 4 patients reported adverse events, 3 from combination therapy and 1 from monotherapy. Edema, gastritis, and abdominal pain were reported in patients treated with combination therapy and giddiness was reported in patients treated with monotherapy. All reported adverse events were of mild-to -moderate in severity. None of the patients reported serious adverse event. The laboratory evaluations were done at baseline and at the end of therapy.

Mean change s from baseline for various laboratory parameters were evaluated at the end of 3 months for all patients. There was non-significant reduction in heart rate at the end of therapy with either treatment. No significant changes from baseline were observed in haematology or biochemistry parameters (Table 4). Changes in blood glucose levels and lipid profile (high-density lipoprotein, low-density lipoprotein, triglycerides, and total cholesterol) were clinically unremarkable across the therapy groups.

Safety Assessment

Side effects found with Atenolol-amlodipine combinations

Tiredness -- in up to 26 percent of people

Low blood pressure (hypotension) -- up to 25 percent

Slow heart rate (bradycardia) -- up to 18 percent

Dizziness -- up to 13 percent

Cold hands or feet -- up to 12 percent

Depression -- up to 12 percent *(see* Atenolol and Depression)

Shortness of breath -- up to 6 percent

Fatigue - up to 6 percent.

Other common side effects of atenolol (occurring in 2 to 4 percent of people) include but are not limited to:

- Leg pain
- A decrease in blood pressure when going from a lying-down or sitting position to standing
- A spinning sensation (vertigo)
- Lightheadedness
- Diarrhea
- Nausea

Side effects found with Nebivolol-amlodipine combination

Headache -- in up to 9 percent of people

Fatigue -- up to 5 percent

Dizziness -- up to 4 percent

Diarrhea -- up to 3 percent

Nausea -- up to 3 percent

Insomnia -- up to 1 percent.

Discussion

The primary goal of treating hypertension is to reduce their blood pressure to target level, which eventually leads to a reduction in the long-term total risk of cardiovascular morbidity and mortality (McKay, 1996). In this regard, although some considerations are necessary before generalizing the results, the present study clearly demonstrated that combination therapy with a β -blocker and a calcium channel blocker is an effective method to achieve the target blood pressure without major safety issues. This randomized, comparative, multicentre, 12 week, outpatient study evaluated antihypertensive efficacy of nebivolol/amlodipine combination in comparison with atenolol/amlodipine alone. The results of this study showed that, combination therapy with nebivolol/amlodipine is superior to atenolol/amlodipine combination therapy with respect to mean fall in SBP, DBP, response rate, and normalization of BP.

After 4 weeks of therapy with atenolol 25 mg , our study reported a fall of -20.6/-10.34 in SBP/DBP which is com parable to that reported in literature (-17.6/-12.5). In our study, for responders after4 weeks of therapy, low-dose combination of nebivolol 5 mg/amlodipine 2.5 mg was found to be superior to low-dose atenolol 25 mg/Amlodipine 2.5mg combination therapy with respect to mean fall in SBP (P = 0.008), mean fall in DBP (P = 0.021) and response rate (P = 0.012).

One reason for combining a calcium antagonist with a β –adrenoceptor antagonist in the treatment of mild to-moderate hypertension is that the latter should improve the patient tolerability of the former by preventing any initial reflex tachycardia which may, in it, because of some adverse effects.

Preliminary studies in stroke-prone spontaneously hypertensive rats have shown that significant synergism exists between atenolol and amlodipine in lowering and stabilizing blood pressure.

The results of present study were confirmed that the combination therapy with Nebivolol/amlodipine is superior to atenolol/Amlodipine combination therapy in patients with mild-to-moderate essential hypertension.

Conclusion

In conclusion, our study has shown that once daily treatment with Nebivolol /amlodipine offers superior antihypertensive efficacy over atenolol/Amlodipine combination therapy in patients with mild-to-moderate essential hypertension.

Conflict of interest

Authors not declare any conflict of interest

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