International Journal of Medical Research & Health Sciences

www.ijmrhs.com Volume 1 Issue 1 Oct-Dec 2012 Coden: IJMRHS
Received: 1th Aug 2012 Revised: 4th Sep 2012 Accepted: 20thSep 2012

Original research article

Comparative effect of fixed dose combination of Amlodipine + Bisoprolol versus Amlodipine and Bisoprolol alone on blood pressure in stage-2 essential hypertensive patients.

*Shirure PA[1] , Tadvi NA[2], Bajait CS[3], Baig MS[4], Gade PR[5]

[1]Dept of Pharmacology, GMC, Nanded, Maharashtra. [2]Dept. of Pharmacology, KIMS, Narketpally, Andhra Pradesh.[3]Dept of Pharmacology, GMC, Nagpur, Maharashtra.[4]Dept of Pharmacology, GMC, Aurangabad, Maharashtra. [5]Dept of Pharmacology, MIMSR Medical College, Latur, Maharashtra.

*Corresponding author Email: drprashantshirure@yahoo.com

Abstract:

Background: Employment of low dose combinations of two antihypertensives, with different mode of action has gained acceptance worldwide for the treatment of mild to moderate hypertension. However, most studies in hypertensive disease have focused on monotherapy. The combination therapy in the treatment of hypertension is largely extrapolated from these monotherapy studies. **Objectives:** To study and compare the effect of amlodipine, bisoprolol and fixed dose combination of amlodipine + bisoprolol on blood pressure in stage-2 essential hypertensive patients. **Methods:** The present study was carried out in Department of Pharmacology in collaboration with Department of Medicine at Government Medical College and Hospital, Aurangabad. **Results and Conclusion :** Amlodipine + bisoprolol in fixed dose combination have showed significant blood pressure control in patients of stage-2 essential hypertension and the antihypertensive effect was greater than individual monotherapy study groups.

Keywords: Amlodipine, Bisoprolol, Hypertension stage-2.

Introduction:

Hypertension is a public health problem as it involves millions of persons in most of the countries (over 50 million in India) and if not treated adequately, results in premature deaths and disability from stroke, heart failure, renal failure and myocardial infarction.[1] The goal of management of hypertension is to detect and control high blood pressure in affected individuals. Modern antihypertensive drug therapy can effectively reduce high blood pressure and consequently, the excess risk of morbidity and mortality from coronary, cerebrovascular and kidney diseases.[2] The traditional approach of therapy advocates beginning with a low dose of a single agent, which is then titrated upward as needed. However monotherapy is successful in only 50-60 % of instances because multiple mechanisms are involved in the pathogenesis of essential hypertension and a single drug class may not inter direct all offending pathways. Also, as higher doses of medication are

administered, there is an increased likelihood of producing untoward side effects and stimulating compensatory mechanisms that partially attenuate the incremental gain in efficacy. [3,4] Drug therapy for hypertension, as with any pharmacological intervention, is to achieve the desired therapeutic response without producing toxicity- maximizing efficacy yet minimizing untoward side effects. Given the emphasis on a "stepped care" approach, drug combinations have been developed that generally contain full-strength doses of each agent and are targeted for individuals whose hypertension fails to respond monotherapy.[4] Single drug therapy, even when maximally titrated, is at best only modestly effective in normalizing blood pressure in stage-1 or stage-2 hypertension, which represents the majority of the hypertensive population. It is increasingly appreciated that the elusive goal of 'normal' blood pressure is achieved only if multiple-drug therapy is employed. The options for multi drug therapy are quite simple, either fixed dose combination therapy or drugs added sequentially one after another to then arrive at an effective multi-drug regimen. Sometimes combination therapy is used to counteract different limbs of pathophysiologic cascade in hypertensive patients with complications or comorbidities.[5] Employment of low dose combinations of two antihypertensives, with different mode of action has gained acceptance worldwide for the treatment of mild to moderate hypertension. The same has also endorsed by JNC-VI and JNC-VII reports which mentions that when the blood pressure is more than 20/10 mm Hg above goal, consideration should be given to initiating with two drugs either as separate prescriptions or in fixed dose combinations.[6] Given that two drugs when used separately are beneficial in a disorder does not necessarily mean that their combination is equally effective or more beneficial.[3] However, most studies in hypertensive disease have focused on monotherapy. The combination therapy in the treatment of hypertension is largely extrapolated from these monotherapy studies.[7] Several studies directly compare different classes of antihypertensives in terms of their efficacy, safety and quality of life, but very few trials compare low dose fixed dose combination therapy with titration of standard dose monotherapy.[8] Present study tried to evaluate the effect of fixed dose combination of amlodipine + bisoprolol versus amlodipine and bisoprolol alone in stage-2 essential hypertensive patients by using low dose combination therapy i.e. an effective and rational alternative for the initial treatment of hypertension when compared with traditional monotherapy.

Objectives: To study and compare the effect of amlodipine, bisoprolol and fixed dose combination of amlodipine + bisoprolol on blood pressure in stage-2 essential hypertensive patients.

Material and methods: The present study was carried out in Department of Pharmacology in collaboration with Department of Medicine at Government Medical College and Hospital, Aurangabad. Sixty patients (n=60) of either sex diagnosed with stage-II essential hypertension attending the medicine outpatient department and satisfying the inclusion and exclusion criteria were enrolled in the study.

Study design: Open parallel, comparative, randomized, controlled, prospective study.

Study duration: The total study duration was four weeks for each patient.

Inclusion criteria: Patients with clinically confirmed stage-II essential hypertension defined as systolic blood pressure ≥ 160 mm Hg and diastolic blood pressure ≥ 100 mm Hg (based on average of two or more readings taken at each of two or more visits) as per JNC-VII classification aged between 40-65 years and willing to give informed consent were included in the study.

Exclusion criteria

Patient with angina pectoris requiring drug therapy with nitrates, beta blockers, calcium channel blockers, or dipyridamole or patient receiving any other antihypertensives.

Patient with a history of myocardial infarction, percutaneous transmural coronary angioplasty

(PTCA) coronary artery bypass grafting (CABG), cerebrovascular accident (CVA), Type -1 Diabetes mellitus or transient ischemic attack (TIA).

Patient with major hematological (SGPT greater than 50% above the upper limits of normal), metabolic, gastrointestinal or endocrine disorders. Patient with serum creatinine greater than 2.5 mg/dl or creatinine clearance less than 50ml/min if available.

Patient with known hypersensitivity to amlodipine or bisoprolol. Woman who are pregnant, lactating of child bearing potential who are not practicing effective methods of contraception. Participation in similar studies within the past one year.

Procedure:: Study protocol was approved by the Ethical Committee of Government Medical College and Hospital, Aurangabad. Patients were explained in detail about the study pattern and related hazards and informed written consent was obtained from the patients. Those included underwent all baseline investigations like complete blood count, liver function tests, kidney function tests, blood sugar level, fundoscopy, ECG, total cholesterol (mg/dl), serum creatinine (mg/dl), SGPT (U/L). Above investigations were done at the **start** of the study and at the **end** of the study. Enrolled patients were divided into three groups of twenty each using computer generated randomization chart in a block of 10's (calculated from True Epistat, Standard version 1999).

Study Groups: Group-1: Amlodipine 5 mg once a day, Group-2: Bisoprolol 5 mg once a day, Group-3: 5 mg Amlodipine + Bisoprolol once a day. All above mentioned drugs are given to patients for 1month therapy. **Concomitant treatment:** No concomitant medication for hypertension was allowed during the study. Patient taking any concomitant medication were recorded.

Follow up: Each patient in respective group was provided free samples for seven days and was asked to visit for (follow up) measuring blood pressure. At each visit patients were assessed for blood pressure control (patient was said to have blood pressure control, when blood pressure reaches to target ≤ 140/90 mm Hg), history pertaining to adverse drug reaction was asked. All patients were given advice about diet and exercise. Refilling of medication was done on every visit. Each patient was assessed for a period of one month, after which all investigations were repeated for comparison. Efficacy was evaluated in the form of control of blood pressure during study. Tolerability was evaluated by noting any adverse drug events during study.

Measurement of blood pressure[6,9,10,11] : At least two measurements were made on two or more separate occasions before labeling subject as hypertensive. American Heart Association recommends two readings with a gap of at least 30 seconds, and the two readings averaged.

Statistical analysis: Statistical analysis was carried out by using paired 't' test for comparing the effect of amlodipine, bisoprolol, and combination on blood pressure during therapy. For comparing between groups after the therapy unpaired 't' test was applied.

Results: Patients (n=60) of stage-2 essential hypertension completed the study. As shown in table-1 for Group I patients the mean systolic blood pressure decreased after 2-weeks i.e. from visit-1 to visit-3 (160.7 ± 13.61 to 153.6 ± 9.65 mm Hg) and the mean diastolic blood pressure also decreased after 2-weeks i.e. from visit-1 to visit-3 (103.4 ± 3.25 to 101.2 ± 4.02 mm Hg) which was not statistically significant ($p < 0.05$) In those patients not responding to amlodipine 5 mg alone, after addition of bisoprolol 5 mg, the mean systolic blood pressure decreased after 2-weeks i.e. from visit-3 to visit-5 (153.6 ± 9.65 to 134^{**} ± 4.81 mm Hg) and the mean diastolic blood pressure also decreased after 2-weeks i.e. from visit-3 to visit-5 (101.2 ± 4.02 to 86.6^{**} ± 2.83 mm Hg) which was highly significant statistically ($p<0.001^{**}$). 80 % of the patients in group-I required addition of bisoprolol for control of blood pressure.

As shown in table-2 the mean systolic blood pressure for Group II patients decreased after 2-weeks i.e. from visit-1 to visit-3 (164.1 ± 4.17 to

161.9 ± 6.72 mm Hg) and the mean diastolic blood pressure decreased after 2-weeks i.e. from visit-1 to visit-3 (105.3 ± 5.03 to 103.5 ± 3.83 mm Hg) which was not statistically significant ($p < 0.05$). In those patients not responding to bisoprolol 5 mg alone, after addition of amlodipine 5 mg, the mean systolic blood pressure decreased after 2-weeks i.e. from visit-3 to visit-5 (161.9 ± 6.72 to 135.2** ± 2.70 mm Hg) and the mean diastolic blood pressure also decreased after 2-weeks i.e. from visit-3 to visit-5 (103.5 ± 3.83 to 86.5** ± 2.03 mm Hg) which was highly significant statistically ($p<0.001$). 90 % the patients required addition of amlodipine for control of blood pressure.

As shown in table-3, for Group III patients , the mean systolic blood pressure decreased after 2-weeks i.e. from visit-1 to visit-3 (164.2 ± 4.62 to 140.8** ± 9.34 mm Hg) and the mean diastolic blood pressure decreased after 2-weeks i.e. from visit-1 to visit-3 (104.6 ± 3.89 to 88.2** ± 4.39 mm Hg) which was highly significant statistically ($p < 0.001$). The mean systolic blood pressure decreased after 2-weeks i.e. from visit-3 to visit-5 (140.8 ± 9.34 to 136.0* ± 8.48 mm Hg) and the mean diastolic blood pressure decreased after 2-weeks i.e. from visit-3 to visit-5 (88.2 ± 4.39 to 86.9* ± 4.07 mm Hg) which was statistically significant ($p<0.05$). 95 % the patients in group-III showed control of blood pressure and only 5 % of the patients required addition of third drug enalapril for control of blood pressure. There were no significant changes from baseline in laboratory parameters like serum creatinine, SGPT, and total cholesterol after therapy in all three-study groups.

Intergroup comparison (Tables 4 and 5)

Visit-1: There was no significant difference in mean systolic and diastolic blood pressure in all three study groups ($p < 0.05$). Visit-3: There was no significant difference in mean systolic and diastolic blood pressure in group-I and group-II ($p < 0.05$). There was reduction in mean systolic and diastolic blood pressure in group-III as compared to group-I and group-II, which was statistically highly significant ($p < 0.001$).Visit-5: No significant difference in mean systolic and diastolic blood pressure was noted in all the study groups ($p < 0.05$).

Table.1: Comparative effect on blood pressure in group-1 (Amlodipine 5mg OD)

Blood Pressure (mm Hg)	**Mean Value Visit-1**	**Mean Value Visit-2**	**Mean Value Visit-3**	**'P'-Value**	**Mean Value Visit-3**	**Mean Value Visit-4**	**Mean Value Visit-5**	**'P'-Value**
Systolic	160.7 ± 3.6	154.7 ±8.0	153.6 ± 9.6	<0.05	153.6 ± 9.6	137.2 ± 5.0	134 ± 4.81**	<0.001
Diastolic	**103.4 ± 3.2**	**99.3 ± 2.8**	**101.2± 4.0**	**<0.05**	**101.2± 4.0**	**86.7± 2.8**	**86.6± 2.83****	**<0.001**

Data presented as Mean±SD. ** P < 0.001- Statistically highly significant

Table.2: comparative effect on blood pressure in group-2 (Bisoprolol 5mg OD)

Blood Pressure (mm Hg)	**Mean Value Visit-1**	**Mean Value Visit-2**	**Mean Value Visit-3**	**'P'-Value**	**Mean Value Visit-3**	**Mean Value Visit-4**	**Mean Value Visit-5**	**'P'-Value**
Systolic	164.1±4.1	159.4±8.6	161.9±6.7	<0.05	161.9± 6.7	138.8±4.6	135.2±2.7**	<0.001
Diastolic	**105.3±5.0**	**101.8±5.3**	**103.5±3.8**	**<0.05**	**103.5± 3.8**	**89.5±3.03**	**86.5±2.03****	**<0.001**

Data presented as Mean±SD. ** P < 0.001- Statistically highly significant

Table-3: Comparative effect on blood pressure in group-3 (Amlodipine + Bisoprolol)

Blood Pressure (mm Hg)	**Mean Value Visit-1**	**Mean Value Visit-2**	**Mean Value Visit-3**	**'P'-Value**	**Mean Value Visit-3**	**Mean Value Visit-4**	**Mean Value Visit-5**	**'P'-Value**
Systolic	164.2±4.6	147.5± 9.5	140.8±9.3**	<0.001	140.8±9.3	136.2± 10.2	136.0±8.4*	<0.05
Diastolic	104.6± 3.8	94.8±6.3	88.2±4.3**	<0.001	88.2± 4.3	87.6±3.7	86.9± 4.0*	<0.05

Data presented as Mean±SD. *P < 0.05- Statistically significant,**P < 0.001 statistically highly significant

Table- 4: Comparative effects on systolic blood pressure in all study groups (Mean ± SD)

Follow up	**Mean Values of Systolic Blood Pressure (mm Hg)**		
	GROUP-1	**GROUP-2**	**GROUP-3**
VISIT-1	160.7 ± 13.61	164.1 ± 4.17	164.2 ± 4.62
VISIT-2	154.7 ± 8.06	159.4 ± 8.63	147.5 ± 9.51
VISIT-3	153.6± 9.65	161.9 ± 6.72	140.8 ± 9.34
VISIT-4	137.2 ± 5.04	138.8 ± 4.69	136.2± 10.25
VISIT-5	134.0 ± 4.81	135.2 ± 2.70	136.0 ± 8.48

Table.5: Comparative effects on diastolic blood pressure in all study groups (Mean ± SD)

Follow up	**Mean Values of Diastolic Blood Pressure (mm Hg)**		
	GROUP-1	**GROUP-2**	**GROUP-3**
VISIT-1	103.4 ± 3.25	105.3 ± 5.03	104.6 ± 3.89
VISIT-2	99.3 ± 2.84	101.8 ± 5.34	94.8 ± 6.30
VISIT-3	101.2 ± 4.02	103.5 ± 3.83	88.2 ± 4.39
VISIT-4	86.7 ± 2.84	89.5 ± 3.03	87.6 ± 3.70
VISIT-5	86.6 ± 2.83	86.5 ± 2.03	86.9 ± 4.07

In the study Group I- Bisoprolol 5 mg & in Group – II Amlodipine 5 mg was added after the end of two weeks.

Discussion : A compelling rational for therapy with low dosages of two agents is to reduce dose related side effects while achieving similar or better pressure control than with full dosages of either agent alone.[4] In order to reduce side effects and improve blood pressure control, combination therapy has been widely accepted but inadequately tested.[12] Present study also showed similar greater antihypertensive effect when bisoprolol was added in group-I and amlodipine was added in group-II as compared to monotherapy in respective groups. L Weiner and G Frithz reported that bisoprolol appears to be an effective antihypertensive agent in mild to moderate hypertension; present study does not substantiate the claim as addition of amlodipine was required to control blood pressure in group-II.[13] The findings of present study was consistent with studies carried out by Lewin A J, Lueg M C, et al.1993;[14] Unzueta-Montoya A, et al, 2003;[15] Prisant L M, 2002;[16] Frishman W H, et.al.1995;[17] as amlodipine 5 mg + bisoprolol 5 mg combination revealed statistically significant reduction in systolic and diastolic blood pressure and no change in heart rate (p < 0.05). Also no clinical significant changes from baseline in

laboratory parameters were observed. Prisant L M, et.al. 1998; in a study reported that mean change from baseline of systolic and diastolic blood pressure for placebo (n=79) was -0.1/-2.2 mm Hg, amlodipine (n=154) -12.4/-10.3 mm Hg, enalapril (n=155) -9.4/-8.2 mm Hg, and bisoprolol/ hydrochlorothiazide (n=155) -14.0/-12.0 mm Hg. Overall efficacy analysis documented a statistically significant decrease in sitting diastolic blood pressure for 10 mg bisoprolol+6.25 mg hydrochlorothiazide compared with placebo, amlodipine and enalapril. There was a significant decrease in sitting systolic blood pressure for 10 mg bisoprolol + 6.25 mg hydrochlorothiazide compared with placebo and enalapril but not amlodipine. Also there was a significant decrease in sitting heart rate for 10 mg bisoprolol+6.25 mg hydrochlorothiazide (-6.2 beats/min) compared with placebo (+0.1 beats/min), amlodipine (+1.2 beats/min) and enalapril (+0.5 beats/min).[18] Findings of our study have showed similar responses but in the low dose of amlodipine 5 mg and bisoprolol 5 mg. Where as the present study does not substantiate the claim of Papademetriou V, et.al. 1998; who reported that the efficacy of low dose combination of bisoprolol and hydrochlorothiazide with amlodipine and enalapril was found to be at least as effective as amlodipine and more effective than enalapril in both men and women.[19]

Conclusion: Amlodipine + bisoprolol in fixed dose combination have showed significant blood pressure control in patients of stage-2 essential hypertension and the antihypertensive effect was greater than individual monotherapy study groups. As this combination has shown excellent response in low doses, this combination can be considered as an alternative to existing strategies in combination therapies for the management of stage-2 essential hypertension.

Acknowledgement: The authors are thankful to the MERCK Pharmaceuticals Ltd. for their assistance in providing free drug samples for the study.

References :

1. Wasir HS. Current trends in management of hypertension. Cardiology Today 1998; 2(5):321-5.
2. Park K. Epidemiology of chronic non-communicable disease and conditions. Park's textbook of preventive and social medicine. 18th ed. Jabalpur : Banaridas Bhanot; 2005:293-8.
3. Franz H. Messerli and Keshav C. Cardiac effects of combination therapy in hypertension. Journal of Cardiovascular Pharmacology 2000; 35 (suppl. 3):S17-S23.
4. William HF, Brain SB, Lewis RC, Vicent LD, Nicolas DV, William JM, Gary D, Judith D G, Demsissie A, Kenneth KA. Multifactorial trial design to assess combination therapy in hypertension. Arch Intern Med. 1994; 154:1461-8.
5. Domenic AS. Rationale for fixed-dose combinations in the treatment of hypertension. Drugs 2002; 62(3):443-62.
6. Aram VC, George LB, Henry RB, William CC, Lee A Green, Joseph LI, Daniel WJ, Barry J M, Suzanne O, Jackson TW, Edward JR. The seventh report of the joint national committee on preventation, detection, evaluation, and treatment of high blood pressure. JAMA – India 2003; 2(6):37-49.
7. Sharma B. Combination therapy in hypertension 2001; 4(2):45-50.
8. Michael LP, Matthew RW, Vasilios P, Michael AW, Issac AA, Demissie A, Martin PL, Albert A C. Low-dose drug combination therapy : An alternative first line approach to hypertension treatment. American Heart Journal 1995; 130(2):359 – 66.
9. Dorothee P, Carlene G, John F, Edward DF, Martha Hill, MaryMc D, Bruce ZM, Human blood pressure measurement by sphygmomanometry. Circulation 1993; 88(5),Part-1:2460-70.

10. Sainani GS. Should every case of mild hypertension be treated with drugs? Cardiology Today 2001; 5(4):233- 40.
11. Daniel WJ, Lawrence JA, Sheldon GS, Edward JR, Claude L. Measuring blood pressure accurately. JAMA-2003; 2(4):68-70.
12. Lessem JN, Singh BN. Calcium channel antagonism and beta blockade in combination: A therapeutic alternative in cardiovascular disorders. Cardiovasc Drugs Ther 1989; 3:355-73.
13. Weiner L, Gfrithz. Antihypertensive effects of bisoprolol during once daily administration in patients with essential hypertension. European Journal of Clinical Pharmacology 1986; 29:517-21.
14. Lewin AJ, Lueg MC, Targum S, Cardenas P. A clinical trial evaluating the 24-hour effects of bisoprolol / hydrochlorthiazide 5 mg / 6.25 mg combination in patients with mild to moderate hypertension. Clin Cardiol 1993; 16(10):732-6.
15. Unzueta-MA, Ordonez T G, Medina-Santillan R. Combined fixed doses therapy in systemic hypertension. Rev Invest Clin 2003; 55(6):635-41.
16. Prisant LM. Fixed low-dose combination in first line treatment of hypertension. J Hypertens. Suppl. 2002; 20(1)S11-9.
17. Frishman WH. First-line therapy option with low dose bisoprolal fumarate and low dose hyrochlorothiazide in patients with stage I and stage II systemic hypertension. J Clin Pharmacol 1995; 35(2):182-8.
18. Prisant LM. Low-dose combination treatment for hypertension versus single drug treatment-bisoprolol / hydrochlorothiazide versus amlodipine, enalapril, and placebo: combined analysis of comparative studies. Am J Ther 1998; 5(5):313-21.
19. Papademetriou V, Prisant LM, Neutel JM, Weir MR. Efficacy of low dose combination of bisoprolol / hydrochlorothiazide compared with amlodipine and enalapril in men and women with essential hypertension AMJ Cardiol 1998; 81(11):1363-5.