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RESEARCH ARTICLE

To Evaluate the Clinical Efficacy of Combination of Low Dose Bisoprolol Fumarate and Low Dose Hydrochlorothiazide with Bisoprolol Alone in Stage I and II Hypertension

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ABSTRACT

OBJECTIVE: Control of hypertension by the use of low dose combination therapy is associated with greater efficacy, less side effects and higher response rates as the result of complementary mechanisms of antihypertensive effect. Present study is an effort to evaluate the efficacy and safety of combined low dose of bisoprolol fumarate and hydrochlorothiazide therapy as compared to bisoprolol alone in stage I and II hypertension.

METHODS: 120 hypertensive patients were taken from the outpatient department of medicine, in tertiary care medical hospital in Northern India. Diagnosis of hypertension was according to Joint National Committee (JNC) VII guidelines. Study was conducted as randomised, controlled open label study over a period of six weeks. Patients were randomly allocated into two groups. Group I patients were started with low dose combination of bisoprolol 2.5 mg and hydrochlorothiazide 6.25mg once daily. Subsequent titration was carried out with bisoprolol up to maximum dose of 10mg with 12.5mg hydrochlorothiazide. Group II was started on bisoprolol alone 5mg and increased up to 20mg according to response. The study parameters were recorded weekly.

RESULTS: At the end of study the mean fall of supine blood pressure for combination was 16.4±4.21/12.73±4.59mmHg and for bisoprolol it was 12.53±3.89/10.13±3.36 mmHg. The difference was statistically significant showing that the combination achieved early and greater reduction in both systolic and diastolic blood pressure with comparatively fewer side effects.

CONCLUSION: The combination of low doses of bisoprolol and hydrochlorothiazide is both safe and effective as compared to bisoprolol monotherapy in the management of Stage I and II hypertension.

KEYWORDS: Bisoprolol, Hydrochlorothiazide, Hypertension, Low-dose combination, Diuretic.

INTRODUCTION:

Hypertension is a major public health problem of worldwide distribution and is a major risk factor for cardiovascular disease morbidity and mortality (1,2). It is responsible for one half of coronary heart disease (CHD) and about two thirds of cerebrovascular accidents (3). The relationship between blood pressure and risk of cardiovascular disease events is continuous, consistent and independent of other risk factors. The higher the blood pressure, the greater the chance of myocardial infarction, heart failure, stroke and kidney disease (4). So detection of hypertension and its effective control are critically important for reducing the risk of heart attacks and strokes as reductions in cardiovascular morbidity and mortality, are well documented with the use of antihypertensive therapy (5,6). In clinical trials, antihypertensive therapy has been associated with 35% to 40% mean reductions in stroke incidence, 20% to 25% in myocardial infarction and more than 50% in heart failure (7). Nowadays, approach to the management involves the use of low dose combinations of different classes of drugs as initial therapy. It has been shown that the addition of a second agent increases response rates from approximately 50% with monotherapy to about 80% with combination therapy (8). The Joint National Committee (JNC VII) on prevention, detection, evaluation and treatment of high blood pressure recommends the combination therapy of a diuretic with beta blocker or angiotensin converting enzyme inhibitor (9). This not only improves compliance but also improves hypertension control, decrease dose dependent side effects and reduces cost of therapy (10). Present study is an effort to compare the efficacy of monotherapy of bisoprolol (beta blocker) to that of low dose combination of bisoprolol and hydrochlorothiazide (diuretic) in hypertensive patients.

MATERIAL AND METHODS:

In this study 120 patients (newly detected cases) of stage I and stage II hypertension were taken from outpatient department of medicine in tertiary care medical hospital in Northern India. Diagnosis of hypertension was done according to Joint National Committee (JNC) VII guidelines (11). Study was done in collaboration with

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medicine department and due permission was taken from concerned authorities.

INCLUSION CRITERIA:

1. Patients with stage 1 and 2 hypertension as per JNC VII guidelines.
2. Patients not on any other antihypertensive drug.
3. Adult males, age 21 years or older and non-pregnant females not planning conception.

EXCLUSION CRITERIA:

1. Females of child bearing age group not planning conception or pregnant.
2. Patients with major comorbidities like hepatic, renal disease, diabetes mellitus or history of stroke, myocardial infarction, cerebral haemorrhage.
3. Contraindications to the use of either drug like cardiogenic shock, overt cardiac failure, second or third degree AV block, marked sinus bradycardia, bronchial asthma, and hypersensitivity to either component or other sulphonamide derived drugs.

Written informed consent was taken from each patient. In order to obtain a uniform pressure reading and to avoid instrumental error all the readings from the right arm were recorded with the same blood pressure instrument and with the same stethoscope. The standard mercury sphygmomanometer was used. The blood pressure readings were taken in supine position. The patients were allowed to lie on bed for five minutes and then the blood pressure and pulse was recorded. All patients after detailed clinical history and thorough physical examination were allocated randomly into two groups, group I and group II.Group I was started on low dose combination of bisoprolol 2.5mg and hydrochlorothiazide 6.25mg once daily. Subsequent titration (7 day interval) was carried out with bisoprolol up to maximum recommended dose of 10 mg with 12.5mg hydrochlorothiazide once daily as appropriate.

Second group was started on standard monotherapy of bisoprolol 5mg. Dose was increased up to 20mg daily according to the effective control of blood pressure. Total duration of therapy was 6 weeks. Routine investigations like fasting blood sugar, total cholesterol, serum creatinine, serum bilirubin were done at the start of the treatment and then after 6 weeks. Periodic observation was done of blood pressure, pulse, subjective improvement and side effects at 1 week interval. The results of observations was statistically analysed by student's't' test. 'p' value less than 0.05 was considered significant.

RESULTS:

The observed mean age of the patients in group I was 48.63±10.03 years and of group II was 44.10±11.82 years, the difference of which was not statistically significant (P>0.05). Regarding gender distribution, Group I had 42 males and 18 females while group II had 34 males and 26 females.

At the completion of six weeks study, administration of combination therapy (Group I) showed fall in mean supine Systolic Blood Pressure (SBP) from 162.73±7.41 to 146.53±6.14 mm Hg (p< 0.001) and mean Diastolic Blood Pressure ((DBP) from 100.06±4.71 to 86.83±4.64 mmHg (p<0.001). Mean fall in SBP was of 16.4±4.21mmHg and in DBP was of 12.73±4.59 mmHg. Patients in Group II on bisoprolol alone showed fall in SBP from 162.53±7.37 to 150.13±9.00 mmHg (p<0.001) and mean DBP from 100.06±4.94 mmHg to 90.60±4.27 mmHg (p<0.001).There was a mean fall in SBP of 12.53±3.89 mmHg and DBP of 10.13±3.36mmHg.

On comparing the mean SBP, administration of combination therapy resulted in decrease by 16.40±4.21 mmHg while with monotherapy decrease in SBP was 12.53±3.89.The difference was statistically highly significant (p<0.001). (Fig.1) On DBP, the net fall with combination was 12.73±4.59mmHg and with bisoprolol was 10.13±3.36 mmHg.Net reduction in DBP with combination was significant (P<0.05) as compared to bisoprolol alone. (Fig.2)

The patients in group I with baseline heart rate 86.06±5.95 beats per minute (bpm) showed a drop to 78.60±6.64 bpm at the end of six weeks while in group II the baseline heart rate of 86.20±5.88 bpm dropped to 75.80±7.37 bpm. The negative chronotropic response to Group II (bisoprolol monotherapy) was greater than that of Group I (combination) by 2.73 beats per minute during the trial and it was statistically significant (P<0.05). (Fig.3) In this study there was no significant change in routine laboratory investigations in both the groups at the start and end of trial.

The side effects with the use of drugs in both the groups are depicted in table 1.

TABLE 1: Reported side effects with the use of drugs.

SIDE EFFECTS	GROUP I (Combination)	GROUP II(Monotherapy)
Bradycardia	0	2
Dizziness	2	2
Fatigue	4	6
Disturbed sleep	2	2
Nausea	0	1

The overall response rate (defined as DBP of ≤ 90mmHg or a mean reduction in DBP of ≥10mmHg from baseline levels) for patients treated with combination was 86.66% and with bisoprolol was 80%

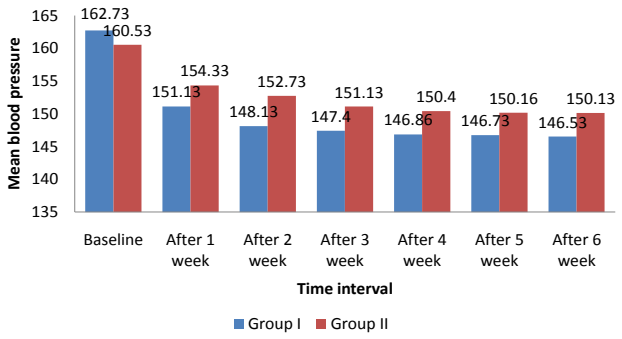

Figure 1: Comparison of Systolic Blood Pressure of Group I and Group II at Different time Intervals

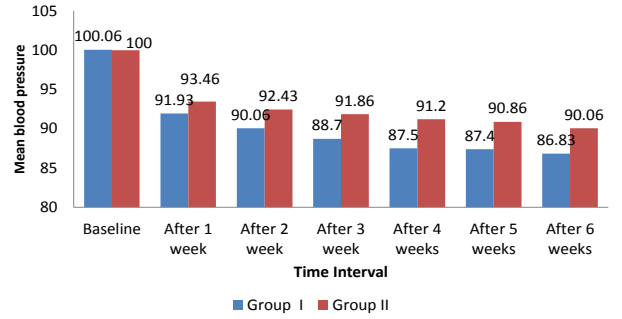

Figure 2: Comparison of Diastolic Blood Pressure of Group I and Group II Patients at Different time Intervals

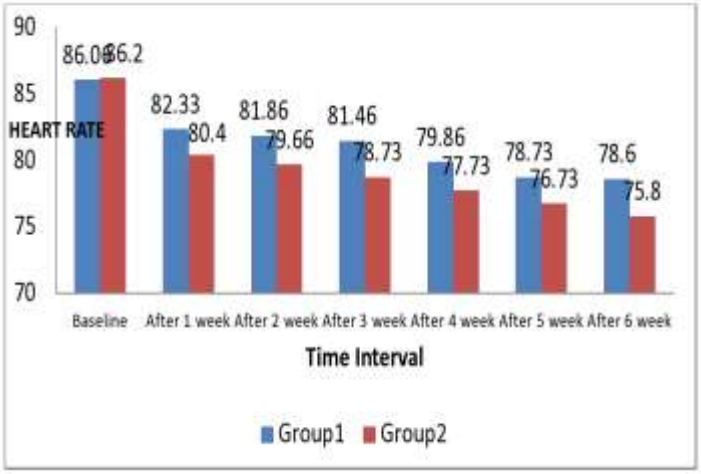

Figure 3: Comparison of Heart Rate of Group I and Group II Patients at Different time Intervals

DISCUSSION:

Hypertension being a multifactorial disease, its management also has to be multipronged, including lifestyle modification and antihypertensive drug therapy (12).The traditional approach to management has been to initiate therapy with a single agent and titrate the dose until adequate control of blood pressure is achieved. This approach has a number of problems and effective control is achieved in only about 50% of patients with monotherapy (13).Also it may not address causes of elevated blood pressure in many patients, since multiple mechanisms are involved in the pathogenesis of hypertension. In addition both effectiveness and adverse effects of most antihypertensive are dose dependent. Therefore, as the dose increases, so do the adverse effects (14).Whereas combination therapy offers a number of advantages over monotherapy. Combination therapy may provide a more broad spectrum approach and may counter the compensatory responses to a single agent. It also allows the use of lower doses of each agent, which can substantially reduce the risk of dose related adverse effects (15).Diuretics have undesirable metabolic effects such as hypokalemia, hyperuricemia, hyperglycemia. These adverse effects may be minimized by reducing the dose of diuretic. It has been shown that these metabolic adverse effects associated with conventional doses of thiazide were not seen with low doses (16).

In the present study mean reduction in SBP was 12.53mm hg and in DSP was 10.13mm hg with bisoprolol in a dose range of 5-20mg at the end of 6weeks.Similarly, study by Frishman et al and Zachariah et al showed a reduction in SBP of 12.6mm Hg, 10.0 mm Hg and in DSP of 10.9mm Hg, 10.5mm Hg at the end of 12weeks/4 weeks with the dose of Bisoprolol 10mg/day and 5mg/day respectively (16, 17). In our study it has been found that the fall in blood pressure both systolic and diastolic was greater with combination (16.4/12.73mm hg) than monotherapy (12.53 /10.13mm hg) and difference was statistically highly significant. The fall was greater with combination at each week of the trial period showing more efficacy of combination over monotherapy. Our results were similar to study by Frishman et al who reported fall of 14.1/10.9mm hg with combination and 13.5/10.9mm hg with monotherapy (18). Another study by Luna et al had also shown the efficacy and safety of low dose bisoprolol/HCTZ combination in 106 patients with mild to moderate hypertension (19). Fewer side effects were seen with combination than monotherapy emphasizing the fact that combining antihypertensive drugs with different modes of action allows smaller doses of drugs to be used

to achieve the control and it minimizes the potential for dose dependent side effects.

CONCLUSION:

Low dose combination of bisoprolol and hydrochlorothiazide causes effective reduction in both systolic and diastolic blood pressure with fewer adverse effects and can be regarded as an appropriate option for the treatment of stage I and stage II hypertension.

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