

Clinical Safety and Efficacy of Combination of Bisoprolol and Hydrochlorothiazide (2.5 mg and 6.25 mg) as Monotherapy in Mild-to-Moderate Essential Hypertension

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Abstract

Aim

To evaluate the clinical efficacy and safety profile of cardioselective β -blocker Bisoprolol (2.5 mg) and diuretic – hydrochlorothiazide (6.25 mg) in combination as monotherapy in patients with mild-to-moderate essential hypertension.

Material and methods

40 patients (30 males and 10 females), in the age group of 30-65 years (mean 70), newly diagnosed hypertensives with mild to moderate essential HTN (sitting SBP 140-179 and DBP > 90-110 mmHg, JNC VI report 1997) attending the medical OPD of GND Hospital, Amritsar were included for the study after obtaining written informed consent. All the cases were subjected to detailed history, clinical examination, lab. investigations including FBS, RBS, B.urea, S.creatinine, S.electrolytes, urinalysis, lipid profile, uric acid, CXR, and 12 leads ECG. Those with secondary/malignant/refractory HTN, congenital/valvular heart disease, stroke, DM, CRF, known hypersensitivity to drugs, and those with concomitant severe illness necessitating other treatment were excluded from the study. A wash-out period of 1 wk. was given at the outset if the patients were taking any other antihypertensive medication(s). After this, BP both SBP and DBP, were taken as the baseline reading. All the cases were given tab. bisoprolol 2.5 mg and HCTZ 6.25 mg in combination once daily as monotherapy in the morning and BP was recorded every week for 4 weeks in the supine and standing position.

Observations

75% were males and 25% females. Mild HTN was observed in 70% and moderate HTN in 30%. The fall in BP (SBP and DBP) both in the supine and standing position at weekly intervals was significant ($p < 0.05$). BP was controlled in 80% of the cases. Side effects were reported in 5% patients in the form of weakness, lassitude, and muscle cramps. These side effects were mild in nature and did not warrant withdrawal of the study drug.

Conclusion

It is concluded that a low dose of cardioselective β -blocker bisoprolol (2.5 mg) and diuretic – HCTZ (6.25 mg) provides greater additive effects with greater efficacy and tolerance, minimal side effects, and lower cost of therapy when used as monotherapy in cases of mild to moderate essential HTN.

Key words

HTN = Hypertension; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; DM = Diabetes mellitus; CRF = Chronic renal failure.

Introduction

Hypertension (HTN) is recognised as a major risk factor for coronary, cerebral, and renal vascular disease¹. About 60 to 80% of deaths attributable to HTN occur in those with mild to moderate HTN². In India, the prevalence of HTN is about 3-15% in urban population and 1-5% in rural population³.

A great stress has been laid on the importance of initiating antihypertensive treatment with monotherapy at the lowest effective dose and then titrating it upward if required, to control BP⁴. The combination therapies in low doses for HTN have been widely accepted due to their synergistic or additive effect, metabolic improvement, or both⁵. The present study was conducted to evaluate the safety and efficacy of combination of cardioselective β -blocker – bisoprolol 2.5 mg and a diuretic - hydrochlorothiazide (HCTZ) 6.25 mg in patients of mild-to-moderate essential HTN as

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once daily dosage. Low dose – HCTZ is known to contribute significantly to the efficacy, safety, and tolerability of low dose bisoprolol resulting in lesser side effects unlike conventional doses of diuretics and β -blocker⁶⁻¹⁰.

Material and methods

40 patients. (30 males and 10 females in the age group of 30-65 years – mean 70 yrs.), newly diagnosed hypertensives with mild-to-moderate essential HTN (sitting SBP > 140-179 mmHg and DBP > 90-110 mmHg, according to JNC VIth report 1997)⁴, attending the medical OPD of GND Hospital, Amritsar comprised the subjects for the study after obtaining written informed consent. BP was measured 3 times in the left arm in the supine position after 10 min. rest and in standing position after 3 min. standing, using a standard mercury sphygmomanometer. A wash-out period of 1 week was given at the outset prior to initiating therapy if the patients were taking any other antihypertensive medication(s). BP recorded (both SBP as well as DBP) at this point of time was taken as the baseline reading. Patients fulfilling the criteria for inclusion had a full work-up which included FBS, RBS, B.urea, S.creatinine, urinalysis, electrolytes, lipid profile, uric acid, X-ray chest, and 12 leads ECG. These parameters were repeated after 4 weeks of therapy to rule out any adverse event. Patients. were excluded if they had any evidence of secondary/malignant/refractory HTN, congenital/valvular heart disease, stroke, diabetes mellitus, chronic renal failure, known hypersensitivity to drugs, and those with concomitant severe illness necessitating other treatment. The cases were given tab. bisoprolol 2.5 mg and HCTZ 6.25 mg in combination once daily in the morning and BP was recorded every week for 4 weeks. Side effects in the form of bradycardia, sick-sinus syndrome, muscle cramps, dizziness, syncope, diabetes mellitus, hyperuricaemia were recorded during each visit. Patients were considered to have responded satisfactorily if they achieved final DBP < 90 mmHg.

Observations

Table I : Showing age distribution.

Age (yrs)	Males	Females
30-39	4	1
40-49	8	1
50-59	15	7
60-65	3	1
Total	30 (75%)	10 (25%)

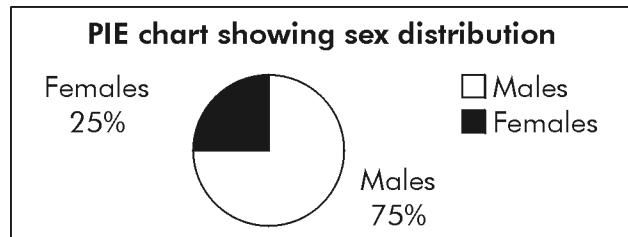


Fig. 1.

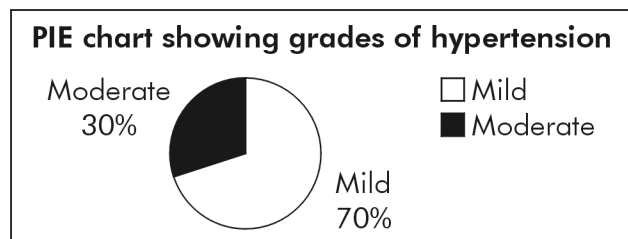


Fig. 2.

Positive family history of HTN was known in 10 (25%) of the subjects, absent in 6 (15%), and not clearly known in 24 (60%). Smoking was detected in 20 (50%) and all were males. Most of the patients were detected by chance – 30 (75%). Symptoms at presentation were headache – 12 (30%), reeling of head – 6 (15%), epistaxis – 3 (7.5%), and palpitations – 3 (7.5%). Out of the 40 patients., 28 (70%) presented with mild HTN and 12 (30%) moderate HTN as depicted in pie chart fig. 2. The average SBP in mild HTN at baseline was 159.2 ± 7.3 and DBP 98.2 ± 2.6 mmHg. In moderate HTN group, SBP and DBP at baseline were 173 ± 10.1 and 101 ± 2.7 mmHg respectively. There were insignificant effects on potassium levels, lipid profile, and glucose tolerance when the investigations were repeated at 4 weeks.

Table II : Showing effects of combination of bisoprolol 2.5 mg and HCTZ 6.25 mg on supine BP (mmHg) through 4 weeks.

n = 40	Basal	Wk 1	Wk 2	Wk 3	Wk 4
Systolic	172.6 ± 3.18	156.1 ± 2.60	152.30 ± 3.17	145.60 ± 2.60	140.10 ± 2.70*
Diastolic	102.18 ± 1.18	95.46 ± 1.17	91.30 ± 1.61	87.12 ± 1.30	83.10 ± 1.81*

* $p < 0.05$ (significant) compared to baseline.

Table III : Showing effects of combination of bisoprolol 2.5 mg and HCTZ 6.25 mg on standing BP (mmHg) through 4 weeks.

n = 40	Basal	Wk 1	Wk 2	Wk 3	Wk 4
Systolic	170.10 ± 3.41	153.30 ± 2.58	146.18 ± 3.21	141.10 ± 2.43	140.30 ± 2.6*
Diastolic	99.85 ± 1.31	91.26 ± 1.12	87.39 ± 1.58	83.42 ± 1.62	81.18 ± 1.30*

* $p < 0.05$ (significant) compared to baseline.

Table IV : Showing reduction in BP from baseline after therapy with bisoprolol and HCTZ in combination.

Position	BP (mmHg)	Wk 1	Wk 2	Wk 3	Wk 4
Supine	Systolic	16.50	20.30	27.00	32.50
	Diastolic	6.72	10.88	15.06	19.08
Standing	Systolic	16.80	23.92	29.00	29.80
	Diastolic	8.59	12.46	16.43	18.67

Discussion

BP is the product of cardiac output and peripheral vascular resistance, both influenced by various factors¹¹. The basal BP (SBP) in supine position fell from 172.6 to 140.10 mmHg at the end of 4 weeks and DBP from 102.18 to 83.10 mmHg at the end of 4 weeks. In this study the BP fall is sustained throughout 24 hrs. period as reported by other workers also^{8,12}. BP was controlled in 80% of subjects with tab. bisoprolol and diuretic - HCTZ in combination given once daily. But other workers have reported the efficacy of combination of bisoprolol and HCTZ to the tune of 61%¹³. So above findings are consistent with the workers reporting 80% efficacy⁷. The mean fall of BP (SBP) in supine position at 1, 2, 3, 4 weeks of therapy was 16.50, 20.30, 27.30, 32.50 mmHg respectively and fall in DBP was 6.72, 10.88, 15.06, and 19.08 mmHg respectively (significant fall). Similarly the mean fall of BP (SBP) in standing position at 1, 2, 3, 4 weeks of treatment was 16.80, 23.92, 29.00, 29.80 mmHg respectively and DBP

fall was 8.59, 12.46, 16.43, 18.67 mmHg (significant fall). Side effects were reported in 5% of patients. in the form of weakness, lassitude, and muscle cramps. These side effects were mild in nature and did not warrant withdrawal of drug. A very low dose of diuretic HCTZ 6.25 mg and cardioselective β -blocker – bisoprolol 2.5 mg provides greater additive effects than would be expected from each drug given separately¹⁴. So a low dose, fixed dose combination of bisoprolol and HCTZ represents a valuable option to initiate the treatment with maximum efficacy, tolerability, and minimum dose related side effects¹⁵.

Conclusion

It is concluded that low dose combination therapy of bisoprolol (2.5 mg) and HCTZ (6.25 mg) is convenient to give as once daily dosing and produces significant reduction in BP with greater efficacy, fewer side effects, improved adherence to treatment, and lower cost of therapy when used as monotherapy in patients. of mild-to-moderate essential HTN.

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