

Efficacy and tolerability of a β -1 selective β blocker, bisoprolol, as a first-line antihypertensive in Indian patients diagnosed with essential hypertension (BRIGHT): an open-label, multicentric observational study

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ABSTRACT

Objectives: This study was aimed to evaluate the efficacy and tolerability of bisoprolol, in Indian patients diagnosed with stage I essential hypertension as first-line drug.

Design: This was an open-label, phase IV, multicentric prospective study.

Settings: 239 outpatient centres across India.

Participants: After ethical approval, patients who were willing to sign informed consent, who are newly diagnosed with JNC VII stage I essential hypertension (systolic blood pressure 140–159 mm Hg or diastolic blood pressure 90–99 mm Hg) and who are prescribed bisoprolol were enrolled in the study. Patients with significant organ disease or complications, women of childbearing age refusing reliable contraceptive method, patients with known contraindications (like symptomatic bradycardia, significant atrioventricular blockade, sick sinus syndrome) and patients with known hypersensitivity reactions to bisoprolol and unwilling patients were excluded.

Primary and secondary outcomes measures: The primary outcome measure was percentage of patients achieving blood pressure (BP) \leq 140/90 mm Hg at the end of 12 weeks, while multiple secondary outcome measures were assessed.

Results: Of 2418 patients screened, 2161 patients were recruited (66.64% men, mean age 51.7 ± 9.8 years, smokers 19.19%) and 2131 (96.44%) patients achieved BP control. There was significant reduction in systolic blood pressure (-25.29 ; SD: 13.22 mm Hg), diastolic blood pressure (-14.14 ; SD: 7.67 mm Hg) and heart rate (-12 /min; SD: 6.15) compared with baseline (all p values <0.05). The median dose of bisoprolol and average period required for the response were 5 mg/day and 33 days, respectively. Bisoprolol was found to be well tolerated in the patients up to 10 mg/day. A total of 1.9% patients showed adverse events, which were mild to

ARTICLE SUMMARY

Article focus

- What is the efficacy of bisoprolol in essential hypertension patients?
- What is the average dose of bisoprolol required for BP control?
- What is the tolerability of bisoprolol in essential hypertensive patients?

Key messages

- Bisoprolol is safe and effective in stage I essential hypertensive patients in India.
- The average dose required was 5 mg/day.
- Target BP was achieved in 96.44% patients.

Strengths and limitations of this study

- First-ever study done for bisoprolol in large Indian population.
- Study re-affirms bisoprolol as first-line drug in the management of hypertension.
- Open-label study.
- Short duration—3 months study.

moderate in severity without any severe adverse event. None required treatment withdrawal.

Conclusion: Bisoprolol is an effective and safe option to control BP. Thus, it can be used as one of the first-line antihypertensive in Indian patients.

INTRODUCTION

Hypertension (HTN) is recognised as a major risk factor for coronary, cerebral and renal vascular disease.^{1–4} It is estimated that 600 million people have HTN worldwide.⁵ In India, the prevalence of HTN is about 20%, of whom 70% have stage I HTN.^{6–8} HTN is

responsible for 57% and 24% of all stroke- and coronary heart disease-related deaths, respectively.⁹ There is a need for increased awareness, diagnosis and management of HTN.

Over the decades, β blockers were used as safe and effective antihypertensives.^{10–12} However, NICE-BSH (National Institute of Clinical Excellence—British Society of Hypertension, 2006) guidelines recommended that β -adrenergic blockers are inferior to other classes of drugs as first-line antihypertensive and that combination of diuretic and a β blocker may lead to precipitation of diabetes. Most of the issues raised by NICE-BSH against β blockers have been observed from less β -1 selective blocker. On the contrary, Reappraisal of European guidelines on hypertension management (2009) suggested that all major antihypertensive drug classes, that is, diuretics, ACE inhibitors, calcium antagonists, angiotensin receptor antagonists and β blockers do not differ significantly for their overall ability to reduce blood pressure (BP) in HTN. They also suggested that there is no undisputable evidence that major drug classes differ in their ability to protect against overall cardiovascular risk or cause-specific cardiovascular events, such as stroke and myocardial infarction.¹³

β -2 Receptor blockade is responsible for various side effects like impairment of glycaemic control, dyslipidemia and erectile dysfunction. β -1 Selective β blockers are effective among patients with natural (mostly younger patients) or induced (smokers) high epinephrine or norepinephrine levels.¹⁴

Bisoprolol is widely studied in the management of essential HTN worldwide. However, it remains to be studied in Indian scenario. This study, BRIGHT (Bisoprolol in Reaching Goals in Hypertension Trial), therefore, was aimed to assess the safety and efficacy of bisoprolol as the first-line therapy against HTN in Indian patients.

MATERIALS AND METHODS

Study design

BRIGHT was designed as an open-label, prospective, multicentric phase IV study.

Ethical considerations

The study protocol was approved by either an Independent Ethics Committee (for all the independent investigators) or Institutional Ethics Committees (for the institutional sites). The study was conducted as per ICH International Conference on Harmonization - Good Clinical Practices (ICH GCP) guidelines 1996 and Indian Council of Medical Research (ICMR) guidelines for the ethical conduct of clinical research in human beings, 2006. A written informed consent was obtained from all the patients before the enrolment.

Study participants

Patients were enrolled from 239 centres across India from May 2010 to July 2010. Those patients who are newly diagnosed with stage I essential HTN as per JNC VII criteria (systolic blood pressure (SBP) 140–159 mm Hg or diastolic blood pressure (DBP) 90–99 mm Hg) and those who were prescribed bisoprolol were enrolled in this study. Patients unwilling to sign informed consent, those with significant organ disease, women of child-bearing age refusing reliable contraceptive method, those presenting with uncontrolled diabetes or diabetic complications as well as those patients with known contraindications, like symptomatic bradycardia, second- or third-degree atrioventricular block, sick sinus syndrome and those with known hypersensitivity reactions to bisoprolol were excluded. Eligible patients were prescribed bisoprolol at an escalating dose (bisoprolol in India is available in four strengths, 1.25, 2.5, 5 and 10 mg). The investigators were suggested to start with lower dose to improve tolerability and compliance towards medication. There was no fixed pattern suggested for dose titration. If there was no adequate BP control with given dose for 4 weeks, then dose was doubled till 10 mg (target) or maximum tolerated dose of bisoprolol. The demographic details and other baseline measures such as cardiac parameters (heart rate (HR), SBP and DBP), metabolic parameters (fasting blood sugar levels, 2-h postprandial blood sugar level and serum cholesterol levels), renal parameters (serum creatinine, creatinine clearance from 24-h urine sample, whenever it was indicated) and safety parameters

Table 1 Visit schedule

Visit Day	V1 Day 0 (baseline)	V2 Week 4	V3 Week 8	V4 Week 12
Informed consent	X			
Demographics and medical history	X			
Screening and inclusion/exclusion	X			
Physical examination	X	X	X	X
Dose titration		X	X	
Vitals, blood pressure and heart rate	X	X	X	X
Investigations	X	X		X
Concomitant medication	X	X	X	X
Adverse events	X	X	X	X

(adverse events (AE)) were recorded. Risk factors like smoking status (whether patient ever smoked or not) were also collected. All the patients were regularly followed on 4th, 8th and 12th week from the date of enrolment (baseline visit). Any significant findings in physical examination, cardiac parameters and safety parameters were noted during all the follow-up visits. Metabolic and renal parameters were re-assessed at the end of 4th and 12th weeks of treatment.

Efficacy and tolerability evaluations

The primary end point, that is, the efficacy of bisoprolol was calculated by response rate. It was defined as the percentage of patients who achieved SBP ≤140 and DBP ≤90 mm Hg at the end of 12 weeks treatment with bisoprolol. The BP was recorded in the sitting position in the right arm, with a standardised mercury sphygmomanometer after 5 min of rest. Similarly, HR was measured in sitting position by measuring radial pulse for 1 min after 5 min rest. The average reduction in the SBP, DBP, average time to reach target BP (in responders), median dose required to control (in responders), average reduction in HR, assessment of compliance at 12 weeks, blood glucose parameters, lipid and renal parameter status from baseline to the end of 12 weeks were assessed as secondary end points. The results for investigations were obtained from local laboratories following the standard procedures. A patient was considered as compliant if he/she consumed at least 80% of the tablets. Tolerability was assessed throughout via AE reporting. The type of AE(s), number of AE(s) and frequency of AE(s) were captured in the case record form (table 1).

Compliance was also evaluated. With a dosing schedule of one tablet per day, 84 (12 weeks) tablets were to be consumed per patient for the overall study period.

Statistical analysis

Descriptive statistics were used to summarise data. The quantitative data were expressed as mean and SD. Qualitative data were analysed by percentages or proportions. Furthermore, to analyse the change in BP and HR over the time, the data were analysed using the analysis of variance followed by Dunnett’s post hoc

Table 2 Demography and vital parameters at baseline

Parameter	N (%) or mean±SD
Age (years)	51.75±9.8
Body mass index (kg/m ²)	25.44±3.8
Heart rate (beats per minute)	85.32±9.14
Systolic blood pressure (mm Hg)	155.59±11.82
Diastolic blood pressure (mm Hg)	95.66±6.95
Men	1440 (66.64)
Women	721 (33.36)
Smokers	430 (19.9)
Non-smokers	1731 (80.1)

testing with baseline as control and paired t test. p Value <0.05 was considered to be significant.

RESULTS

Patient demography and baseline data

Of total 2418 patients screened, 257 patients were not enrolled in the study either due to failure to meet the inclusion criteria or due to refusal to give informed consent. A total of 2161 patients were enrolled and analysed in this study. The demographic and baseline data of the patients are given in table 2.

Of all patients enrolled, 1440 (66.64%) were men and 430 (19.9%) were smokers. The response rates at the end of 2nd week were 40.77%, and it increased by an additional 26.19%, 17.82%, 11.66% during 4th, 8th, and 12th week, respectively. Thus, the response rate at 12 weeks was 96.44%. The mean SBP was significantly reduced from baseline 155.59 to 130.29 mm Hg (−25.29 mm Hg) at the end of 12 weeks of treatment with bisoprolol (SD: 13.22; p<0.05). Similarly, there was significant reduction in DBP (−14.14 mm Hg) after the 12 week of treatment (SD: 7.67; p<0.05). The mean HR was also found to be significantly reduced from 85.34 to 73.28 (−12.06) beats per minute after the treatment (SD: 6.15; p<0.05) (table 3).

Metabolic parameters

Table 4 highlights the baseline and 12-week data of the patients enrolled and followed up in the BRIGHT study.

Subgroup analysis was done for smokers and younger hypertensive patients on bisoprolol. Although the overall

Table 3 Haemodynamic parameters at various time points during the study

Visit schedule	SBP (mm Hg) Mean±SD	DBP (mm Hg) Mean±SD	HR (beats per minute) Mean±SD
Baseline	155.59±11.82	95.66±6.95	85.32±9.14
2 weeks	144.44±12/07	89.25±6.65	79.35±7.98
4 weeks	138.18±12.01	85.47±6.23	76.35±7.48
8 weeks	133.54±11.22	83.04±5.77	74.32±6.52
12 weeks	130.29±10.87	81.52±5.23	73.28±6.33
Change at 12 weeks from baseline (%)	−25.29 (−16.26)	−14.14 (−14.78)	−12.05 (−14.12)

p Value for all parameters <0.05.
DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

Table 4 Change in metabolic parameters during the treatment with bisoprolol

Parameter	At baseline	At the end of follow-up	Average difference from baseline
Fasting blood sugar (mg/dl)	100.9±19.2	95.1±17.2	-5.8
Postprandial blood glucose (2-h after food; mg/dl)	140.92±27.49	132.59±20.21	-8.32
Total cholesterol (mg/dl)	194.7±22.0	176.2±69.2	-18.5
Triglycerides (mg/dl)	166.5±44.3	153.5±53.3	-13
Low-density lipoprotein (mg/dl)	120.3±38.7	110.2±27.5	-10.1
High-density lipoprotein (mg/dl)	43.6±20.6	46.2±29.4	2.6
Serum creatinine (mg/dl)	0.97±0.22	0.93±0.20	-0.04
Creatinine clearance (ml/min)	94.5±23.08	92.58±23.03	-1.98

The values are represented as mean±SD, and there was no deterioration in any of the measured parameters as per paired t test. For all the parameters p<0.05, except creatinine clearance (p=0.09).

response rates in smokers (96.75%) and non-smokers (94.17%) were similar (p=0.275), a higher number of smokers responded to bisoprolol within 2 weeks (45.35% vs 39.17%). Furthermore, smokers had a greater reduction in HR at the end of 12 weeks (-13.79 vs -11.99 beats per minute; p<0.05, table 5).

Similarly, younger patients (age <50 years) showed a greater reduction in SBP/DBP (-25.81/-14.31 vs -24.53/-13.67 mm Hg; p<0.05, table 6).

Compliance

About 98.76% of patients were compliant, defined as those consuming more than 80% of tablets as recommended by the treating physician. BP was found to be controlled in 1622 (80.9%) patients at the dose of 5 mg/day. In patients, in whom control was achieved, an average of 33 days was required to reach the target BP of <140 and 90 mm Hg.

Adverse events

During the study period, 41 (1.9%) patients reported mild AEs, which mainly included dizziness, headache, fatigue, nausea and vomiting. No patient developed any serious AE. Treatment withdrawal was not requested by any patients nor deemed required by any of the physicians.

DISCUSSION

The initial drug management of HTN is a contentious issue. The Report of the Joint National Committee on

detection, evaluation and treatment of high BP also recommends β blockers as one of the initial antihypertensive agents.¹⁵ β Blockers have become one of the first choice drugs for antihypertensive therapy in various countries, unless there are any clinical conditions contraindicating their use. Recently, there has been a consensus paper published on ‘The role of β blockers in the management of HTN: an Asian perspective’.¹⁶ This review found that β blockers are still one of the first-line antihypertensive drugs in many Asian countries.

From the old concept of managing HTN by A or B+ C or D (initiation by either ACE inhibitor/angiotensin II receptor blocker (ARBs) or a β blocker and addition of either calcium channel blocker (CCB) or a diuretic in case of monotherapy failure), we have come a long way where data have proven all drug classes to be therapeutically equivalent. This has also been proposed by European Society of Cardiology - European Society of Hypertension (ESC-ESH) reappraisal, 2009. Thus, it is imperative that any class proposed to be first-line antihypertensive should be equally effective in clinically differing subgroups of hypertensive patients.^{17 18} While initiating a β blocker in hypertensive patient, physicians should make a choice based on effective lowering of BP to a target of 140/90 mm Hg, protection over 24 h, selectivity to β-1 blocker, metabolism independent of CYP2D6, balanced clearance (eg, half liver/half kidney) and prevention of ‘new-onset’ heart failure and coronary events.

Table 5 Change in haemodynamic parameters in smokers and non-smokers, expressed as mean±SD

Parameter	SBP		DBP		HR	
	Smoker	Non-smoker	Smoker	Non-smoker	Smoker	Non-smoker
Baseline	156.2±12.22	155.34±11.71	95.64±7.26	95.65±6.84	85.64±9.07	85.25±9.17
2 weeks	146.06±12.65	145.15±32.32	89.40±6.87	89.034±6.48	79.87±8.58	79.76±18.59
4 weeks	139.39±12.65	137.82±11.87	85.52±6.29	85.32±6.12	76.55±6.88	76.31±7.65
8 weeks	134.49±12.13	133.27±11.01	82.87±5.73	83.03±5.67	74.10±6.64	74.38±6.38
12 weeks	130.37±11.64	130.26±10.74	81.59±4.85	81.53±5.33	72.66±6.20	73.42±6.38
Change in SBP at 12 weeks versus baseline	-25.82	-25.07	-21.4	-20.91	-13.73*	-11.99

*p Value <0.05. DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

Table 6 Change in haemodynamic parameters in young (<50 years) and old (≥50 years) patients, expressed as mean±SD

Parameter Visit schedule	SBP		DBP		HR	
	Young	Old	Young	Old	Young	Old
Baseline	156.45±11.78	154.32±11.81	95.88±7.00	95.25±6.23	85.91±9.98	84.73±9.23
2 weeks	146.63±38.79	143.65±11.94	89.17±6.16	89.08±6.30	80.19±23.19	79.24±8.28
4 weeks	138.88±12.23	137.14±11.61	85.45±5.96	85.39±6.09	76.43±7.03	76.28±7.74
8 weeks	133.9±11.30	132.99±11.07	83.17±5.19	83.06±5.68	74.23±6.77	74.32±6.28
12 weeks	130.64±10.93	129.79±10.77	81.56±4.78	81.57±4.90	73.33±6.36	73.2±6.28
Average change from baseline	-25.81*	-24.53	-14.31*	-13.67	-12.58	-11.53

*p Value <0.05.

DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

In our study, response rate of 96.44% was achieved (BP ≤140 mm Hg and 90 mm Hg) at the end of 12 weeks treatment with a median dose of 5 mg/day of bisoprolol. Although a small percentage of the patients did not respond to bisoprolol, this number was lower (3.56%) compared with other therapies.¹⁹ In our study subgroups as well, the reduction in BP was significant, irrespective of age, gender, smoking status, body mass index, HR and baseline BP.

It is noteworthy to mention that all the therapeutic classes have some typical 'class-related' side effects. While ACE inhibitors are known to cause cough, CCBs can cause pedal oedema, diuretics can cause electrolyte imbalance, non-selective β blockers can cause AE such as fatigue, depression, impaired exercise tolerance, sexual dysfunction and asthma attacks.²⁰ Although β blockers have their efficacy proven for controlling BP and HR, their effect on blood glucose, cholesterol and quality of life has always been questioned. Bisoprolol, one of the highest β-1 selective β blocker, reduces BP and HR and is largely devoid of these side effects.^{21–28}

In the BRIGHT study, we found favourable changes in the levels of metabolic and renal parameters. There was a reduction in the glucose level (fasting blood sugar level and postprandial blood sugar level) and improvement in lipid profile (total cholesterol, triglycerides, low-density lipoprotein and high-density lipoprotein) at the end of bisoprolol treatment. However, we suggest that these changes may not be ascertained to bisoprolol therapy as other confounding factors (reducing salt intake, alcohol avoidance, multifactorial diet control, weight reduction, tobacco cessation, physical exercise and stress management) were not captured.^{29–31}

This is the first study, to our knowledge, to demonstrate the efficacy and tolerability of bisoprolol in large number of Indian patients in real world scenario. The BRIGHT study also confirms the consistency of therapeutic efficacy of bisoprolol even after 25 years of its approval to be used in the management of HTN.

Although this was a large observational study that added significantly to the efficacy and safety of a β-1 selective β blocker, it could not answer clearly the difference of using this drug in patients with probably high epinephrine and nor-epinephrine levels (smoker

and younger patients) compared with the other group. This study being an open-label study, the possibility of placebo effect should be considered. In an analysis of 354 randomised studies, it was found that single drug given at full dose will cause average reduction in 9.1 mm Hg SBP and 5.5 mm Hg DBP.³² However, we would like to draw attention towards comparative study of atenolol and nebivolol. In this study for 6 months, SBP reduced from 160.13±1.62 mm Hg to 118.93±0.87 mm Hg in atenolol arm and from 159.93±1.62 mm Hg to 116.73±0.91 mm Hg in nebivolol. Similar responses were observed with DBP and HR.³³ Thus, whether Indian patients are highly responsive to β blockers or there is contribution by placebo effect needs to be investigated further.

This study reflects the real-life scenario, which is often missed out in well-designed randomised studies. The changes in metabolic parameters are unlikely to be related to bisoprolol, as it was found to be 'metabolically neutral' in previous studies.^{34–35} These metabolic changes would suggest significant improvement in the lifestyle conditions; which could not be measured by the given study design. Although bisoprolol is found to be an effective drug in varying clinical situations, we would still suggest a prospective randomised controlled study of longer duration, adequately powered to measure metabolic and renal outcomes as primary end points.

CONCLUSION

The BRIGHT study showed that bisoprolol can be used effectively as first-line treatment for the patients diagnosed with stage I essential HTN.

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