Management Practices in Indian Patients with Uncontrolled Hypertension

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Abstract

Hypertension (HTN), being a major risk factor for cardiovascular diseases (CVDs), is an important issue of medical and public health. High blood pressure (BP) is ranked as the third most important risk factor for attributable burden of disease in south Asia (2010). Hypertension (HTN) exerts a substantial public health burden on cardiovascular health status and healthcare systems in India. Uncontrolled hypertension among adults with hypertension is associated with increased mortality. An inadequate data is available in India on uncontrolled hypertension.

Objectives: The present study was planned to evaluate the patient profile, co-morbidities, management in uncontrolled hypertensive patients and also to determine the number of patients with resistant hypertension across India.

Methods: A total of 4725 uncontrolled hypertensive patients who were on anti-hypertensive medications were evaluated in this cross-sectional and observational study. The observed patterns were recorded with respect to the prevalence of uncontrolled hypertension and evaluate the socio-demographic, medical history, anthropometric variables and treatment preferences in Indian patients with uncontrolled hypertension.

Results: Majority of the patients with uncontrolled hypertension were males (71.4%) and aged 46-65 years. Most of the study population were pre-obese (males: 35.7%; females: 27.4%). Higher proportion of patients with uncontrolled hypertension were residents of Maharashtra (25.6%) and Gujarat (11.6%). Antihypertensive monotherapy was used by 45.4% and 54.6% patients used combination therapy (≥ 2 categories of anti-hypertensive medications). Angiotensin receptor blockers (ARBs) were the most preferred agent as monotherapy (70.6%) and also the most common component of dual and triple combination anti-hypertensive agent. 19.5% (922/4725) patients had resistant hypertension and 80% of the patients were aged 46-65 years. Higher proportion of patients were males (67.2%; 620/922) and higher proportion of patients were to residents of Andhra Pradesh (21.4% patients) and Maharashtra (19.3% patients). All 922 resistant hypertensive patients were on ≥ 3 anti-hypertensive medications and received ARB + CCB + Diuretics as the

Editorial Viewpoint

• Uncontrolled hypertension among adults with hypertension is associated with increased mortality.
• All the resistant hypertension patients were on ≥3 antihypertensive drugs.
• The protective measures to be taken to control hypertension include diet and physical activity, regular patient follow-up and counselling, and improvement in drug adherence.

Introduction

Hypertension is considered as one of the major risk factors of cardiovascular (CV) morbidity and mortality.¹ It affects approximately 26% of the population worldwide.² It is responsible for at least 45% of deaths due to heart disease and 51% of deaths due to stroke; accounting for 9.4 million deaths worldwide every year.³⁻⁵ In India, its prevalence varies from 20-40% in urban adults to 12-17% in rural adults. It is estimated that the number of people with hypertension will increase to 214 million by 2025.
most preferred anti-hypertensive combination therapy. Diabetes and dyslipidaemia were the major comorbidities reported in patients with uncontrolled and resistant hypertension. Lipid lowering agents followed by oral hypoglycaemic agents and antiplatelet medications were the common concomitant medications used. Various factor responsible for not achieving the desired blood pressure goals may be the patient's lack of awareness about recent hypertensive treatment guidelines that might contribute to patient's poor adherence due to not explaining adequately the benefit and risks of a medication, not giving consideration to the patient's life style, the cost of medication, and inadequate dose titration.

**Conclusion:** Uncontrolled hypertension is a major problem in India. It is prudent to focus on multiple risk factors while treating hypertension. A combination therapy with multiple blood pressure lowering drugs are important and concerns should be identified while selecting the appropriate dosage of combinations of anti-hypertensive therapy and adherence to the therapy. The preferred choices for mono, dual combination and triple combination anti-hypertensive regimens are ARBs; ARB + CCB; ARB + CCB + Diuretics, respectively. In this study, most of the patients were on monotherapy; however a rationale combination therapy or dose adjustment is required for the effective management of hypertension. The protective measures to be taken to control hypertension includes reduction of physicians inertia, diet and physical activity, regular patient follow-up with BP measurements and counselling, and the improvement in patient adherence.

with equal prevalence in men and women. In India, cardiovascular disease (CVD) is estimated to be responsible for 1.5 million deaths annually and it is estimated that by 2020, CVD will be the largest cause of mortality and morbidity.\(^5\) Recent community surveys conducted on uncontrolled hypertension demonstrated that more than 1 in 5 adults have uncontrolled hypertension.\(^6\)

The family history of dyslipidaemia, diabetes and cigarette smoking are the major risk factors associated with hypertension. The initial approach to hypertension management is lifestyle changes, including dietary interventions (reducing salt intake, increasing potassium intake, avoiding alcohol and multifactorial diet control), weight reduction, tobacco cessation, physical activity and stress management. Current antihypertensive therapy includes diuretics, β-blockers (BB), calcium channel blockers (CCBs), angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).\(^7\) Previous literature have reported the clear benefits of antihypertensive therapy in lowering CV mortality and morbidity by modest reduction in diastolic and/or systolic blood pressure (BP).\(^8,9\) Despite the availability of effective treatments, BP is adequately controlled in minor proportion of the patients.\(^10-12\) The reason for uncontrolled hypertension may be physicians' non-aggressive and a conservative approach for hypertension treatment. The EISBERG project found that physicians were more focussed to lower diastolic BP, despite the proven significance of systolic BP in CV risk.\(^13\) Another widely recognized reason for inability to achieve BP targets, despite being on antihypertensive medications was patients' poor compliance or adherence to therapy. The EISBERG project reported that 70% of the primary care physicians believed that patients’ poor compliance was the major reason for uncontrolled hypertension.\(^13\) The persistence with therapy varies between different classes of antihypertensive drugs; it was significantly higher in patients receiving angiotensin II type 1 receptor compared to other antihypertensive drugs.\(^14\)

Improvement in BP control leads to a reduction in substantial number of CV events. As per the NHANES data more than half of the individuals with uncontrolled hypertension are not on any antihypertensive medications;\(^15\) however, meta-analyses of randomized controlled trials reported that antihypertensive therapy reduces the risk of stroke by approximately 30%, CHD by 10-20%, CHF by 40-50%, and total mortality by 10%.\(^16\) Studies have identified several factors related to poor blood pressure control which may be patient or physician related. Patient-related factors include access to health care, compliance, and comorbidities while physician-related factors include knowledge base, perceptions about the care delivered, and practice patterns. Uncontrolled hypertension have been associated with various characteristics such age, obesity, and lack of exercise. Race is related to hypertension control as it may interact with multiple factors such as access to care, susceptibility to hypertension, and comorbid conditions. Patient noncompliance may contribute to poor blood pressure control.\(^17\)

A patient with uncontrolled hypertension develops resistant hypertension when the BP level is above the goal inspite of concurrent use of 3 antihypertensive agents of different classes (one agent should be a diuretic). These patients with resistant hypertension can have controlled BP levels if treated with ≥4 medications. The prevalence of resistant hypertension is approximately 20-30%. Old age, obesity and high baseline systolic BP are the most common risk factors for uncontrolled and
resistant hypertension.\(^{18}\) Resistant hypertension can be treated by identification and reversal of lifestyle factors (dietary salt restriction, weight loss, cessation or reduction of alcohol intake, increased physical activity, ingestion of high fibre, potassium and calcium containing diet), appropriate treatment of secondary causes of hypertension (obstructive sleep apnea, renal artery stenosis) and by the use of multiple antihypertensive medications.

There are limited studies on patients with resistant hypertension as these patients have a high CV risk, are generally associated with multiple diseases and tough enrolment. In absence of any large data from India, the exact prevalence of resistant hypertension is still unknown. Hence, the present study was planned to explore the prevalence of resistant hypertension and evaluate the socio-demographic, medical history, anthropometric variables and physician treatment preferences in Indian patients with uncontrolled hypertension.

**Material and Methods**

**Study design**

This was a cross-sectional, multi-centric, non-interventional, observational and single visit study conducted across 486 sites in India during the year 2013-2014. The eligibility criteria included male and female patients with uncontrolled hypertension, who were on anti-hypertensive therapy, aged between 18 to 65 years, visited for a routine visit to their physician and were willing to sign the patient authorization form. Those patients who required hospitalization for any cause or were pregnant or lactating were excluded from the study. Uncontrolled hypertension was defined as inability to achieve the systolic blood pressure <140 (mmHg) and diastolic blood pressure <90 (mmHg) as per Joint National Committee VII guidelines, despite being on anti-hypertensive medications. Resistant hypertension was defined as blood pressure that remains elevated above treatment goals despite concurrent use of 3 anti-hypertensive medications of different classes that includes a diuretic.\(^{19}\)

The final protocol was approved by respective institutional ethics committee. The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization of Good Clinical Practice guidelines, Indian Council of Medical Research, Indian GCP guidelines, and approved protocol.

**Study assessments**

During the routine visit to the physician, the investigator or his/her designee collected the patient data on Abbott data collection form to gather information on patient’s socio demographic factors (age, gender, state of residence, education and occupation), lifestyle practices (smoking, alcohol consumption, tobacco chewing, and diet), medical history (diabetes, hypertension, ischemic heart disease, congestive heart failure, chronic kidney disease, dyslipidaemia and hormone replacement therapy in women), treatment history of anti-hypertensive medications like BB, alpha blockers, ACE inhibitors, ARBs, diuretics, centrally acting drugs, CCBs and others, vital parameters (systolic and diastolic BP and pulse rate), anthropometric variables (weight, height, waist and hip circumference, and body mass index [BMI]), and concomitant medications (oral contraceptive pills, non-steroidal anti-inflammatory drugs, steroids, oral hypoglycaemic drugs, lipid lowering agents, antiplatelet medications, and others).

**Study Endpoints**

The primary study endpoints were demographic and anthropometric variables, medical history, and vital parameters. The secondary study endpoints were treatment history, current treatment and concomitant medications used. In addition, patients with resistant hypertension were evaluated in terms of their demographic characteristics, medical history and current treatment.

**Statistical analysis**

No formal sample size calculation was done as this was an observational and non-interventional study. All enrolled patients constituted the analysis population. The statistical analysis was done using Statistical Analysis System\(^{\circ}\) version 9.3 software. The continuous variables were summarized descriptively by mean, standard deviation, median and range. The categorical variables were described by frequencies and percentages.

**Results**

**Patient Demographics**

A total of 4814 patients with uncontrolled hypertension were assessed for eligibility. Of these, 4725 (98.2%) patients who met the eligibility criteria were enrolled in this study, and constituted the analysis population. The mean age, weight, height, waist circumference, hip circumference, and BMI of the patient population was 51.2 ± 8.64 years, 71.6 ± 11.77 kg, 162.3 ± 9.10 cm, 90.5 ± 10.29 cm, 96.6 ± 13.97 cm, and 27.3 ± 4.41 kg/m\(^2\), respectively. The systolic, diastolic BP and pulse rate of the patient population was 158.70 ± 14.498 mm Hg and 97.93 ± 9.352 mm Hg, and 83.16 ± 8.373 bpm, respectively. The majority of the patients were educated (post-graduates/higher secondary/secondary; 57.2%), vegetarians (71.5%), non-smokers (83.9%), non-alcoholic (86.6%), non-tobacco chewers (90.3%) and had an outdoor lifestyle (68.3%). The mean duration of smoking, alcohol consumption, and tobacco chewing was 14.52 ± 9.196 years, 13.37 ± 8.537 years, and 13.55 ± 8.787 years, respectively. Higher proportion of patients were residents of Maharashtra (25.6%)
and Gujarat (11.6%). Majority of the population (71.4%, 3376/4725) were males and aged 46-65 years. Majority of the patients (both males and females) were pre-obese (males: 35.7%; females: 27.4%) and higher proportion of females were obese than males in age category 46-65 years (23.8% versus 16.9%). Patient’s demographics are summarized in Figure 1. Vital signs are presented in Table 1.

Of 4725 patients with uncontrolled hypertension, 922 (19.5%) patients with mean age 52.6 ± 8.25 years had a resistant hypertension. 80% of the patients were aged 46-65 years. The higher proportion of patients were males (67.2%; 620/922), educated (63%) and employed (52.4% patients). Higher proportion of patients were residents of Andhra Pradesh (21.4%), Maharashtra (19.3%), Rajasthan (13.9%) and Uttar Pradesh (12.8%). The mean BMI was comparable between males and females.

Diabetes and dyslipidemia were the major comorbidities reported in patients with uncontrolled and resistant hypertension. Both the disorders were majorly reported in patients of age category 46-65 years.

**Current Treatment**

Anti-hypertensive monotherapy was used by 45.4% (2147/4725) patients and 54.6% (2578/4725) patients used the combination therapy (≥ 2 categories of anti-hypertensive medications) where 1497 (58.1%) patients, 879 (34.1%) patients, 179 (6.9%) patients, 22
Angiotensin receptor blockers (ARBs) were the most commonly used anti-hypertensive drugs (57%; 244/4197 patients) followed by Olmesartan (21% patients) and Telmisartan (11.5% patients). Amlodipine (CCB) (66%; 334/4197 patients) and Hydrochlorothiazide (80%; 416/879 patients) were the most commonly used dual drug combinations. Olmesartan + Amlodipine + Hydrochlorothiazide was the most common triple drug combination; Amlodipine + Hydrochlorothiazide + Metoprolol (BB) + Olmesartan (46%; 58/179 patients) was the most common 4 drug combination; Amlodipine + Enalapril (ACE inhibitor) + Hydrochlorothiazide + Metoprolol + Olmesartan was the most common 5 drug combination (23%; 5/22 patients); and 1 patient used the combination of Amlodipine + Atenolol + Enalapril + Hydrochlorothiazide + Olmesartan + Prazosin. State-wise, the most common dual drug combination was CCB + ARB in the state of Maharashtra (28% patients) and Gujarat (44% patients), BB + ARB in the state of Andhra Pradesh (38% patients), and Diuretics + ARB in the state of Rajasthan (54% patients). The most common triple drug combination was Diuretics + CCB + ARB across Maharashtra (47% patients), Andhra Pradesh (84% patients), Gujarat (35% patients), and Rajasthan (50% patients).

All 922 resistant hypertensive patients were on ≥ 3 anti-hypertensive medications; 732 (79%), 167 (18%), 22 (2.4%) and 1 (0.1%) patients were on combination of 3, 4, 5 and 6 anti-hypertensive medications, respectively. CCB + ARB + diuretics (71%; 522/732 patients), CCB + BB + ARB + diuretics (75%; 126/167 patients), CCB + BB + ACE inhibitor + ARB + diuretics (73%; 16/22 patients), and CCB + BB + alpha blockers + ACE inhibitors + ARB + diuretics (1 patient) was the most commonly used triple, 4, 5 and 6 drug combinations, respectively.

**Concomitant Medication**

The data of concomitant medications was available for 1284/4725 (27%) patients. Lipid lowering agents (59%; 751/1284 patients) followed by oral hypoglycaemic agents (51%; 652/1284 patients) and antiplatelet medications (23%; 301/1284 patients) were the common concomitant medications used by the patient population. More than 20% of the patients were on concomitant medications.

**Table 1: Summary of vital signs**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>158.70 ± 14.498</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>97.93 ± 9.352</td>
</tr>
<tr>
<td>Pulse rate (bpm)</td>
<td>83.16 ± 8.373</td>
</tr>
</tbody>
</table>

(0.9%) patients, and 1 patient used dual, triple, 4, 5 and 6 drug combinations, respectively.
on Metformin (32% patients), Atorvastatin (30% patients), Rosuvastatin (27% patients) and Glimepiride (23% patients).

Discussion

Previous studies have reported varied prevalence of hypertension across different states in India; 7.24% in rural Maharashtra, 3% in Rural Sevagram, 7.8% in Mumbai hospitals, and 8.6% in an urban slum Tirupathi. In this study, majority of uncontrolled hypertensive patients were among the residents of Maharashtra and Gujarat which could possibly be due to environmental factors and lifestyle differences in different geographical regions in India.

Factors such as age, BMI, obesity, diabetes, smoking, alcohol and tobacco intake, dietary habits, lifestyle and stress are the common risk factors for hypertension. Old or increasing age is one of the strongest risk factor associated with uncontrolled and resistant hypertension, which could be possibly because of atherosclerotic changes occurring in blood vessels with aging, especially under stress, unknown factors and increased prevalence of risk factors of hypertension in males. In this study, 73% of the patients had uncontrolled hypertension and 80% of the patients had resistant hypertension in the age group of 46-65 years. Obesity is another risk factor associated with uncontrolled and resistant hypertension. Most of the patients in our study were either pre-obese or obese and there was a significant correlation of increasing body weight with hypertension. These observations were in concordance with 2 epidemiology studies conducted in Chennai and Bangalore reporting age, obesity and gender as the strongest risk factors for hypertension. The mean BMI in the present study was 27.3 ± 4.41 kg/m², which was much higher than the suggested cut off of 23 kg/m² in Asian Indian adults, which suggests overweight as the main modifiable risk factor. Alcoholism and smoking history was present in 13.4% and 16.1% of the study population. Our results were in concordance to the earlier reported study where alcohol and cigarette addiction was reported in 13.2% of the hypertensive patients.

The causes of uncontrolled hypertension may be either patient related or physician related. Patient related factors includes restricted access to healthcare, increased susceptibility to hypertension (advanced age and obesity), noncompliance with therapy (knowledge deficits, medication cost, complicated regimens, side effects, poor physician patient communication and lack of social support), and resistant hypertension. On the contrary, physician factors includes inadequate knowledge about guidelines (BP threshold, isolated systolic hypertension, threshold for diabetic patient, use of monotherapy in patients in whom BP is difficult to control), overestimation of adherence to guidelines, disagreement with guidelines, concern about medication side effects, belief that office BP trends to be higher than home BP, reluctance to treat an asymptomatic condition and lack of time at office visits. Despite recognizing that BP are elevated, physicians may choose not to advance therapy. Several reasons have been suggested for this clinical inertia such as overestimation of adherence to guidelines, lack of practice supports to facilitate the achievement of target BP, and use of soft justifications to avoid advancing care for asymptomatic patients.

Indians have excessive dietary salt ingestion due to consumption of ethnic Indian foods like chutneys, papads, and pickles which are the regular household choices that increase daily sodium consumption and predisposes the population to hypertension followed by uncontrolled and resistant hypertension. Excessive dietary sodium intake leads to development of resistant hypertension by either directly increasing the BP or decreasing the BP lowering effect of most of the antihypertensive agents. Overall, 19.5% of the patients with uncontrolled hypertension developed resistant hypertension.

Recent years have witnessed a rapid increase in the prevalence of diabetes and hypertension in India with diabetes being one of the major comorbidities in hypertensive patients, which may be attributed to the increasing levels of sedentary lifestyle, urbanization, and consumption of energy rich and poor fiber food. Screening India's Twin Epidemic (SITE) study have shown that diabetes and hypertension coexists in 21% patients; concluding the double jeopardy of diabetes and hypertension to blast an explosion of CV complications. These reports are further substantiated by an epidemiology study conducted in Chennai, where diseases like diabetes, obesity, hypercholesterolemia, hypertriglyceridemia, abdominal and general obesity were higher in hypertensive patients as compared to normotensive patients. We also observed diabetes to be the major comorbidity associated with uncontrolled (47%) and resistant hypertension (34%). Other comorbid conditions observed were dyslipidemia, ischemic heart disease, chronic kidney disease, congestive heart failure, hormone replacement therapy which are reported to occur in hypertensive patients.

Antihypertensive therapy, including ACE inhibitors, ARBs, CCBs, diuretics and newer a-blockers, have shown clear benefits in terms of reducing the CV mortality and morbidity. In 1995, Materson et al. reported additive antihypertensive benefit by combination of 2 medications of different classes. Few earlier reports
have also suggested significant additional antihypertensive benefit of ACE inhibitor + ARB/CCB over monotherapy with different agents.\(^{33,34}\) In 2013, it was reported that BP target goals can be achieved with two or more drugs in 60-70% of patients.\(^{35}\) In this study, 45% patients received monotherapy while 55% patients received combination therapy; suggesting that combination therapy is required in most of the patients with hypertension. It is important to find out the right monotherapy or combination therapy with appropriate doses for each individual hypertensive patient.\(^{36}\) In 2000, Chaput compared persistency of ARBs over other antihypertensive agents in 25000 patients included in a Canadian database and reported that the that persistence was significantly higher among patients treated with ARBs compared to other antihypertensive medications by 24 months.\(^{14}\) This study also reported the similar results where ARBs (Olmesartan and Telmisartan) were the most commonly used agents as monotherapy or a component of combinations therapy; which may be due to its higher persistence owing to its better tolerability and effectiveness over other antihypertensive agents. The combination of ARBs, with CCBs and/or Diuretics is the commonly used antihypertensive in hypertension management.

**Conclusion**

Uncontrolled hypertension is a major problem in India. A number of factors contribute to the variation in hypertension control. The reason for poor control is the heterogeneous population including patient characteristics (age, obesity), co-morbid conditions, concomitant medicines, and treatment patterns which presumably contribute directly to control blood pressure. It is prudent to focus on multiple risk factors while treating hypertension. A combination therapy with multiple BP lowering drugs is important and concerns should be identified while selecting the combinations of anti-hypertensive that are less effective on the basis of efficacy and tolerability. Co-morbid conditions such as dyslipidemia or diabetes are majorly associated with uncontrolled and resistant hypertension. Thus special attention is required for those with hypertension co-existing with diabetes mellitus and dyslipidaemia since poor control of both conditions increases their risk for cardiovascular complications. Monotherapy is the leading trend of anti-hypertensive therapy followed by dual combination and triple combination anti-hypertensive regimens. The preferred choices for mono, dual combination and triple combination anti-hypertensive regimens are ARBs; ARB+ CCB; ARB + CCB + Diuretics respectively. The preferred anti-hypertensive therapy for resistant hypertensive patients is triple combination of anti-hypertensive regimen ARB + CCB + Diuretics. In this study, most of the patients were on monotherapy; however a rationale combination therapy or dose adjustment is required for the effective management of hypertension. The protective measures to be taken to control hypertension includes reduction of physicians inertia, diet and physical activity, regular patient follow-up with BP measurements and counselling, and the improvement in patient adherence.

**Acknowledgements**

The authors would like to thank all doctors who participated in this study. The authors would also like to acknowledge site management organization & medical writing agency (Max-Neeman International) and data management agency (Prism Biomed) for their efforts.

**Disclosure**

This study was funded by Abbott Healthcare Pvt. Ltd. Dr. Abhijit Trailokya, Chief Manager-Medical Services, Dr. Kalpesh Dalvi, Medical Advisor-Medical Services, Mr. Suhas Talele, Manager-Clinical Research, Medical Services all are employees of Abbott Healthcare Private Limited, Mulund, Mumbai.

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