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Study on Resistant Hypertension in a Tertiary Care Centre in Malabar

K.G. Sajeeth Kumar[1], Abhay John Gray[2], AdarshAayiliath K[3]
[1] *Kerala University of Health Sciences, Professor, Department of General Medicine, Govt. Medical College, Calicut*
[2] *Kerala University of Health Sciences, Junior Resident, Department of General Medicine, Govt. Medical College, Calicut*
[3] *Kerala University of Health Sciences, Senior Resident, Department of General Medicine, Govt. Medical College, Calicut*

Abstract:
Background*: Resistant hypertension is defined as blood pressure that remains uncontrolled in spite of concurrent use of three antihypertensives of different classes. The true prevalence of resistant hypertension is not known, studies suggest it includes approximately 10–15% of the general hypertensive population. Resistant hypertension is associated with increased mortality and only few studies are available on resistant hypertension from India.*
Objectives: *To study the demographic factors, clinical profile and comorbidities among patients with resistant hypertension in a tertiary care centre in north Kerala.*
Methods: *An observational study was conducted among patients with resistant hypertension admitted in Department of General Medicine in Government Medical college, Calicut over a period of one year from June 2017 to May 2018. A total of 488 cases were obtained and data regarding demographics, clinical profile and comorbidities were collected. Data was analyzed with SPSS software.*
Results: *Of the 488 patients, there were 283(58%) males and 205 (42%) females. Mean age was 59.46 ± 4.28. Mean systolic BP was 157.45 ± 6.28 and mean diastolic BP was 97.19 ± 5.63. 350 (71.7%) of patients had Chronic kidney disease, 161 (33.1%) had diabetes and 143 (29.3) patients had obstructive sleep apnea. 169 (34.6%) patients had dyslipidemia. Mean number of drugs required to control BP was 4.52 ± 0.65. 260(53.2%) patients were overweight/obese.*
Conclusions: *Males have higher prevalence of resistant hypertension than females. Majority of patients with resistant hypertension had chronic kidney disease (71.7%). Obesity is a major risk factor of resistant hypertension. Life style modifications are essential in addition to pharmacological measures for adequate control of BP.*
Key Word: *Resistant hypertension, Demographic factors, Obesity*

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I. Introduction

Resistant hypertension is defined by a blood pressure of at least 140/90 mm Hg or at least 130/80 mm Hg in patients with diabetes or renal disease despite adherence to treatment with full doses of at least three antihypertensive medications, including a diuretic(1). The term "resistant hypertension" indicates that the patient has true resistance to otherwise effective antihypertensive treatment and not other causes including improper blood pressure measurement, an inadequately prescribed antihypertensive regimen, failure to adhere to adequately prescribed therapy, or hypertension that is elevated in the office but normal at home (white coat hypertension)(2). Although arbitrary in regard to the number of medications required, resistant hypertension is thus defined in order to identify patients who are at high risk of having reversible causes of hypertension and/or patients who, because of persistently high blood pressure levels, may benefit from special diagnostic and therapeutic considerations(3).

While the exact prevalence of resistant hypertension is unknown, cross-sectional studies suggest that it includes approximately 10–15% of the general hypertensive population(4). In an analysis of National Health and Nutrition Examination Survey (NHANES) participants being treated for hypertension, only 53% were controlled to <140/90 mm Hg. NHANES participants with chronic kidney disease, only 37% were controlled to <130/80 mm Hgand only 25% of participants with diabetes were controlled to <130/85 mm Hg(5)

Inaccurate measurement of blood pressure can result in the appearance of treatment resistance. Measuring the blood pressure before letting the patient sit quietly and use of too small a cuff will result in falsely high blood pressure readings.

Poor adherence to antihypertensive therapy is a major cause of lack of blood pressure control. Approximately 40% of patients with newly diagnosed hypertension will discontinue their antihypertensive medications during the first year of treatment.(6)

Studies indicate that a significant white-coat effect (when clinic blood pressures are persistently elevated while out-of-office values are normal or significantly lower) is as common in patients with resistant hypertension as in the more general hypertensive population, with a prevalence in the range of 20% to 30%(7)

The diagnosis of resistant hypertension depends upon an accurate measurement of the blood pressure. Resistant hypertension can only be distinguished from white coat hypertension by out of office blood pressure measurements. This is best accomplished with 24-hour ambulatory monitoring(8).

Patient characteristics associated with resistant hypertension include older age, high baseline blood pressure, obesity, excessive salt ingestion, chronic kidney disease, diabetes, left ventricular hypertrophy, black race, female sex. The strongest predictor of treatment resistance was having CKD as defined by a serum creatinine of $\geq$1.5 mg/dL.

Lifestyle factors associated with resistant hypertension mainly include obesity, dietary salt, alcohol and drug related causes. Obesity is a common feature of patients with resistant hypertension. Mechanisms of obesity-induced hypertension are complex and not fully elucidated but include impaired sodium excretion, increased sympathetic nervous system activity, and activation of the renin-angiotensin-aldosterone system(9). Excessive dietary sodium intake contributes to the development of resistant hypertension both through directly increasing blood pressure and by blunting the blood pressure–lowering effect of most classes of antihypertensive agents. These effects tend to be more pronounced in typical salt-sensitive patients, including the elderly, African Americans, and, in particular, patients with CKD(10).

Medications that interfere with blood pressure control include nonsteroidal anti-inflammatory agents including aspirin, sympathomimetic agents (decongestants, diet pills, cocaine), alcohol, oral contraceptives, cyclosporine, stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine), erythropoietin, natural licorice, some herbal compounds. Given their widespread use, nonnarcotic analgesics, including nonsteroidal anti-inflammatory agents (NSAIDs), aspirin, and acetaminophen, are probably the most common offending agents in terms of worsening blood pressure control(11). Meta-analyses of the effects of NSAIDs have indicated average increases in mean arterial pressure of approximately 5.0 mm Hg(12). NSAIDs can blunt the blood pressure–lowering effect of several antihypertensive medication classes, including diuretics, ACE inhibitors, angiotensin receptor blockers (ARBs), and β-blockers(13)

Patients with resistant hypertension have to be screened for secondary causes of hypertension. The most common are primary aldosteronism and renal artery stenosis, chronic kidney disease, and obstructive sleep apnea. Less common causes include pheochromocytoma, Cushing's syndrome, and aortic coarctation. The likelihood of a readily definable secondary cause of hypertension is greater in older patients because of a greater prevalence of sleep apnea, renal parenchymal disease, renal artery stenosis, and possibly primary aldosteronism(14)

Treatment of resistant hypertension include both pharmacological and non-pharmacological measures. The main non-pharmacological modalities include a lower salt diet, weight loss in obese and overweight patients, and moderation of alcohol intake. The pharmacologic treatment of resistant hypertension, by definition, involves combinations of three or more drugs, including a diuretic. The choice of agents should be individualized and may depend upon consideration of prior benefit, history of adverse events, financial limitations, and the presence of concomitant disease processes such as chronic kidney disease or diabetes. In those with little renal impairment, chlorthalidone is preferred to hydrochlorothiazide for the treatment of resistant hypertension(15). If blood pressure is uncontrolled on three drugs aldosterone antagonist like spironolactone can be added. In trials spironolactone therapy has significantly decreased the mean daytime and nighttime ambulatory systolic blood pressures(16). If the patient is still hypertensive, additional medications are added sequentially. Possible agents that may be used include vasodilating beta blockers (labetalol, carvedilol or nebivolol), centrally acting agents (clonidine or guanfacine), and direct vasodilators (hydralazine or minoxidil). If beta blockers are used, a vasodilating beta blocker, such as labetalol, carvedilol or nebivolol, may provide more antihypertensive benefit with fewer side effects compared to traditional beta blockers(17).

The recent advances in the treatment of resistant hypertension include Catheter-based radiofrequency ablation of renal sympathetic nerves and Electrical stimulation of carotid sinus baroreceptors. In the Symplicity-HTN-2 trial Catheter based radiofrequency ablation demonstrated significant reduction in systolic blood pressure(18). In the Rheos Pivotal Trial Electrical stimulation of carotid sinus demonstrated nonsignificantly large decrease in the systolic blood pressure(19).

Patients with resistant hypertension remain at increased risk for target organ damage, morbidity, and mortality despite ongoing antihypertensive drug therapy(20). Heart failure, stroke, myocardial infarction, and renal failure are related to the degree of the elevation in blood pressure.

Despite the high prevalence, only few studies are published on resistant hypertension from India and south India. Most of the studies available are conducted in the western population. Etiological factors and clinical profile in the Indian scenario may not correlate with theirs. This study aims to look into the demographic factors, clinical profile and comorbidities of patients with resistant hypertension.

II. Materials And Methods

This cross-sectional study was conducted over a period of 1 year from June 2017 to May 2018 in a tertiary care center in north Kerala. Of the patients presenting to the department of general medicine, those who were on at least three antihypertensives were selected. A diuretic was required to be part of the regimen. Patients not giving consent and not adhering to treatment were excluded from the study.

Of the selected patients accurate measurement of the blood pressure was done manually. The patients were advised to sit quietly for three to five minutes before taking the measurement. BP cuff of correct size was used with arm held at level of heart. The blood pressure was measured in both arms, with the arm with the higher pressure being used to make future measurements.

A pre tested questionnaire was given to the patients. Demographic factors of the patients- age and gender, medical history including number and class of antihypertensive drugs, comorbidities and clinical data were collected. BMI of the patients were calculated. Relevant blood investigations were done.Patients with BMI 25-29.9 were considered overweight and BMI 30 and more were taken as obese.

Data analysis was done using SPSS software.

III. Results

A total of 488 patients participated in the study. There were 283 (58%) males and 205 (42%) females. Male to female ratio was 1:1.3. Majority of the study population were in the age group 60-64 yrs. Mean age was 59.46 ± 4.28.

Table no 1: Age Distribution in patients with Resistant Hypertension

AGE GROUP	MALE	FEMALE
45-49	6	3
50-54	31	24
55-59	101	73
60-64	123	83
65-69	19	20
70 and above	3	2

Most of the patients had systolic BP between 150 – 159 and diastolic BP between 90 – 99. Mean systolic BP was 157.45 ± 6.28 and mean diastolic BP was 97.19 ± 5.63.

Majority of the study population had one or more comorbidities. Chronic kidney disease was the most common co morbid disease seen in the study population followed by dyslipidemia. 72% of patients with resistant hypertension in the study sample had chronic kidney disease.

Table no 2: Co-morbidities in patients with Resistant Hypertension

CO-MORBID DISEASE	NUMBER OF PATIENTS	PERCENTAGE
CKD	350	72%
DYSLIPIDEMIA	169	35%
DIABETES	161	33%
OBSTRUCTIVE SLEEP APNOEA	143	29%

Of the study population, 148 patients were overweight (30.3%) and 112 patients were obese (22.9%). 260 patients (53.2%) had BMI more than 25.

Majority of the patients had BP controlled on 4 drugs (55.7%). Mean number of drugs required to control BP was 4.52 ± 0.65.

Table no 3: Number of drugs needed for Blood pressure control

NUMBER OF DRUGS	NUMBEROF PATIENTS
4	272
5	179
6	34
7	3

IV. Discussion

In the study population 58% patients were males. In previously published studies like Prevalence of Resistant Hypertension in the United States 2003-2005 by Stephen D Peresell females were more (53.8%)(21). Also in studies Resistant Hypertension: patient characteristics, risk factors, co-morbidities and outcome A Oliveras& A de la Sierra female patients were 54%(22). In the study Resistant hypertension patient characteristics and risk of stroke Chen-Ying Hung, Kuo-Yang Wang female population was 50.9%(23). In our study male patients with resistant hypertension were significantly more, which is possibly due to difference in geography and study population.

In this study mean age was 59.46 ± 4.28. In studies Prevalence of resistant hypertension in the United States 2003-2005 by Stephen D Peresell and Resistant hypertension: patient characteristics, risk factors, co-morbidities and outcomeA Oliveras& A de la Sierra mean age was around 66.

Diabetic patients represented 33% of the study population, which was comparable with the previous studies.

Of the 488 patients with resistant hypertension studied, chronic kidney disease (72%) was the most common comorbidity. It was significantly higher on comparison with previous studies. In the study Refractory hypertension: Definition, Prevalence, and patient characteristics by Maria Acelajado patients with chronic kidney disease was only 24.1% (4). Also in the study Resistant hypertension, Patient Characteristics and Risk of Stroke the incidence of chronic kidney disease was significantly lower(23). These studies were from Western countries and is the possible reason for discordant results

In the study 260 patients (53%) were either overweight or obese. Obesity was proposed to be an important life style risk for Resistant hypertension in many previous studies like Resistant Hypertension: Diagnosis, Evaluation and Treatment by David A Calhoun(3).

Obstructive sleep apnea was seen in 29% of the study population. In the study Refractory hypertension: Definition, Prevalence, and patient characteristics by Maria Acelajado Obstructive sleep apnea was seen in 31% of the patients, which is almost comparable.

Dyslipidemia was seen in 35% of the study population. Study of Lipid Profile in Hypertension Penjuri Naresh, Ashok Kumar E it was observed that there is significant alteration in lipid profile in hypertensive patients comparing with controls(24).

Obesity produces resistant hypertension, in addition also is a major risk factor for insulin resistance and metabolic syndrome. So, in addition to pharmacological measures lifestyle modifications also play an important role in reducing blood pressure. Patients must be advised to adapt DASH diet; physical activity and weight reduction must be encouraged.

Proper drug adherence of the patients must be ensured. Many patients who were excluded from the study were poorly adherent to the drug either due to side effects or cost of the drug.

Resistant hypertension especially in young patients should be worked up for a secondary cause because it can change the course and prognosis of an otherwise incurable disease.

V. Conclusion

Males have higher prevalence of resistant hypertension than females. Majority of patients with resistant hypertension had chronic kidney disease (71.7%). Obesity is a major risk factor of resistant hypertension. Life style modifications are essential in addition to pharmacological measures for adequate control of BP.

Limitations

The study was an observational study, so association between risk factors and resistant hypertension couldn't be established. It was a hospital-based study and may not fully represent the community. BP recording was done manually, ambulatory BP measurement couldn't be used. Cases of white coat hypertension couldn't be fully excluded

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