



Clinical Evaluation Of Patients Of Resistant Hypertension

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ABSTRACT

Resistant hypertension is a common clinical problem faced by both primary care clinicians and specialists. The joint National Committee 7 defines resistant Hypertension as failure to achieve goal B.P. (< 140/90 mm Hg for the overall population & < 130/80 mm Hg for those with diabetes mellitus or chronic kidney disease) when a patient adheres to maximum tolerated doses of 3 or more antihypertensive drugs including a diuretic¹. Causes of true resistant hypertension include Chronic Kidney Disease (CKD), Obesity, obstructive sleep apnea, volume over load, drug induced hypertension NSAID use, excessive alcohol intake².

A cross sectional observational study consisting of 40 patients of resistant hypertension, was undertaken to study clinical profile and to evaluate various causes of resistant hypertension. Most common associated co-morbid condition was CKD (52.5%), followed by IHD (15%). Less common conditions were Renal artery stenosis (12.5%), CVA (12.5%), SLE (5%), Coarctation of aorta (2.5%), COPD (2.5%) and IgA Nephropathy & Nephritic syndrome (2.5%) each. Common risk factor for resistant hypertension were Tobacco use (35%), Smoking (32.5%), alcohol (10%), Sedentary life style (7.5%), Chronic NSAIDs use (2.5%) and High salt diet (2.5%). Effective management of resistant hypertension requires careful examination for and exclusion of factors associated with pseudo resistance, identification and when possible, modification of factors related to true B.P. elevation.

KEYWORDS : Resistant, Hypertension, CKD, Obesity.

INTRODUCTION: Resistant hypertension is a common clinical problem faced by both primary care clinicians and specialists. The joint National Committee 7 defines resistant Hypertension as failure to achieve goal B.P. (\leq 140/90 mm Hg for the overall population & \leq 130/80 mm Hg for those with diabetes mellitus or chronic kidney disease) when a patient adheres to maximum tolerated doses of 3 antihypertensive drugs including a diuretic¹. The true prevalence or resistant hypertension is not known. Post hoc analyses of clinical trials suggest a prevalence of 10% to almost 30% of Hypertensive patients. As older age and obesity are two strongest risk factors for uncontrolled hypertension, the incidence of resistant hypertension will likely increase as the population becomes more elderly and obese².

It is important to distinguish between apparent (Pseudo) & true resistant hypertension. The term Pseudo resistance refers to lack of B.P. control with appropriate treatment in a patient who doesn't have resistant hypertension³.

factors include :

1. Suboptimal BP measurement technique
2. Inadequate doses of antihypertensive drugs
3. Inappropriate choice of antihypertensive combination
4. Poor communication and lack of desire to invest in patient education
5. White-coat effect
6. Poor adherence to prescribed therapy
7. Side effects of antihypertensive medication
8. Complicated dosing regimens
9. Memory or psychiatric issues or poor cognition (especially in elderly patients)
10. Costs of drugs (in some healthcare systems)

Causes of true resistant hypertension include causes of secondary hypertension, obstructive sleep apnea, Volume overload, excessive alcohol intake, drug induced hypertension and obesity.

Effective management of resistant hypertension requires, a careful

examination for & exclusion of factors associated with pseudo – resistance, identification and when possible, modification of factors related to true B.P. elevation. After all of these are successfully managed, and aggressive treatment regimen designed to compensate for all mechanisms of BP elevation in a given patient most importantly to control volume overload with proper use of diuretics will help in moving toward effective BP control for the majority of patients. The benefits of successful treatment, likely substantial as suggested by hypertension outcome studies in general and by the early Veterans Administration cooperative studies, which demonstrated a 96% reduction in cardiovascular events over 18 months with severe hypertension

There are no studies specifically powered to address the prognosis of persons with resistant hypertension. However, as evident from all population studies on Hypertension related target organ damage, the risk of myocardial infarction, stroke, heart failure, & renal failure directly relate to the level of B.P. Expanding our understanding of the causes of resistant hypertension and thereby potentially allowing for more effective prevention and / or treatment will be essential to improve the long-term clinical management of this disorder⁴.

Causes of Resistant Hypertension:

1. Obesity : 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 system⁵.

2.Excessive Dietary Salt: Excessive dietary sodium intake contribute 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. Meta-analyses of clinical trials recommends the sodium restriction to approximately 1.7g/day in mild uncomplicated hypertension. The antihypertensive effects of sodium restriction are even more pronounced in patients with resistant hypertension. 24 Hour ambulatory blood pressure was reduced by 23/9 mm Hg when

sodium intake was decreased to 1.1g/day in patients with resistant hypertension⁷.

3. Alcohol: Heavy alcohol intake is associated with both an increased risk of hypertension, as well as treatment-resistant hypertension. Cessation of heavy alcohol ingestion by a small group of patients reduced 24-hour ambulatory systolic blood pressure by 7.2 mm Hg and diastolic blood pressure by 6.6 mm Hg while decreasing the prevalence of hypertension from 42% to 12%⁸.

4. High fat diet & low fiber diet: A significant reduction in blood pressure may also occur with a low fat intake or with a high fiber intake. Combining these dietary measures of high fiber, low fat and low sodium regime has also been reported to produce a significant reduction of systolic and diastolic blood pressure with reduction of antihypertensive drug therapy.

5. Non-Steroidal anti-inflammatory agents (NSAIDs): Two large prospective cohort studies in normotensive women reported higher risks of subsequent hypertension among NSAIDs users than in women without regular NSAIDs. In the first study, the risk of developing hypertension was increased about two times in women using acetaminophen. In the second study, women with frequent use of nonnarcotic analgesics had statistically significant higher risk for developing hypertension. Another large, case-control study revealed a 66% increased risk for initiating antihypertensive drugs in NSAIDs users compared to nonuser¹⁰.

6. Oral contraceptives: Oral contraceptives represent another class of drugs that are widely used and are capable of inducing hypertension. The larger study evaluating the effects of oral contraceptives on blood pressure was the Nurses' Health Study, in which more than 60,000 normotensive women had 80% higher risk of developing hypertension compared to women those were not using such drugs. Combined oral contraceptives (progestin and estradiol), which were widely used in the past, were associated with blood pressure elevations more frequently than progestin only oral contraceptives. On the contrary, drospirenone reduces blood pressure when combined with estradiol.

7. Sympathomimetic agents: Use of Decongestants, diet pills, cocaine, dexmethyl phenidate, dextroamphetamine, amphetamine, methamphetamine, modafinil were associated with associated with higher blood pressure.

8. Obstructive sleep apnea: Obstructive Sleep apnea is particularly common in patients with resistant hypertension. Several studies have reported an extremely high prevalence of OSA in patients with resistant hypertension. Two decades ago, a Swedish study of 16 patients with resistant hypertension reported a 56% prevalence of OSA in these patients compared to 19% in patients with controlled hypertension. In a study of 41 consecutive resistant hypertensives, an 83% prevalence of unsuspected OSA was found. A well-described mechanism by which sleep apnea being both more common and more severe in the men compared with women patients. A well-described mechanism by which sleep apnea contributes to the development of hypertension in that the intermittent hypoxemia, and /or increased upper airway resistance associated with sleep apnea, induces a sustained increase in sympathetic nervous system (SNS) activity. Increases in SNS output would be expected to raise blood pressure through increases in cardiac output and peripheral resistance as well as by increased fluid retention⁹.

9. Chronic kidney disease : (CKD) is both a common cause and complication of poorly controlled hypertension. In a recent cross-sectional analysis of patients with CKD being followed in nephrology clinics, less than 15% had their blood pressure controlled to <130/80 mm Hg despite the use on average of 3 different antihypertensive agents. Treatment resistance in patients with CKD is undoubtedly related in large part to increased sodium

and fluid retention and consequential intravascular volume expansion¹¹.

10. Renal Artery Stenosis: Renovascular disease is a common finding in hypertensive patients undergoing cardiac catheterization, with more than 20% of patients having unilateral or bilateral renal artery stenosis. The former series suggested that 12.7% of patients ≤ 50 years of age referred to a hypertension center had a secondary cause of hypertension, the most common of which (35%) was renovascular disease. Bilateral renal artery stenosis should be suspected in patients with a history of "flash" or episodic pulmonary edema, especially when echocardiography indicates preserved systolic heart function¹².

11. Diabetes Mellitus: Diabetes and hypertension are commonly associated, particularly in patients with difficult-to-control hypertension. Clinical trials have indicated that in order to achieve the lower blood pressure goal recommended for patients with diabetes, an average range of 2.8 to 4.2 antihypertensive medications will be needed. Pathophysiologic effects attributed to insulin resistance that may contribute to worsening hypertension include increased sympathetic nervous activity, vascular smooth muscle cell proliferation, and increased sodium retention¹³.

12. Primary Aldosteronism (PA): Recent studies indicate that primary aldosteronism is a much more common cause of hypertension than had been demonstrated historically. Several studies performed in the last decade report a much higher prevalence of PA (>10%), suggesting an "epidemic" of this condition. In study of more than 400 Czech patients with moderate-to-severe hypertension, the prevalence of PA was (19%)¹⁴.

13. Pheochromocytoma: Pheochromocytoma represents a small but important fraction of secondary causes of resistant hypertension. Pheochromocytoma is characterized by increased blood pressure variability, related to the level of norepinephrine secretion by the tumor¹⁵.

14. Cushing's syndrome : Hypertension is present in 70% to 90% of patients with Cushing's syndrome. Although the main mechanism of hypertension in Cushing's syndrome is overstimulation of the nonselective mineral corticoid receptor by cortisol, other factors such as sleep apnea and the insulin resistance are major contributors to hypertension in this disease prevalence of resistant hypertension in patients with Cushing's syndrome because the pathogenesis of hypertension in Cushing's syndrome involves activation of mineral corticoid receptors, the usual antihypertensive agents employed in treating primary hypertension may not be effective in lowering blood pressure to goals. Surgical excision of an adrenocorticotrophic hormone (ACTH)-or cortisol-producing tumor-effectively lowers blood pressure. The most effective antihypertensive pharmacological agent in Cushing's syndrome is a mineralo corticod receptor antagonist¹⁶.

Materials and Methods: This cross sectional observational study was conducted at the medical college, department of general medicine at tertiary care hospital.

- 40 patients (OPD as well as IPD) with diagnosis of resistant hypertension during period of December 2012 to November 2014 were included in the study.

Inclusion criteria:

- Patients of Hypertension with blood pressure $\geq 140/90$ mm Hg in patients other than diabetic and chronic kidney disease.
- BP $\geq 130/80$ mm Hg in diabetic and chronic kidney disease patients.
- Those who are taking 3 or more antihypertensive drugs including a diuretic.

Exclusion Criteria:

Patients with hypertensive emergencies like intracranial bleed, Acute myocardial infarction etc.

OBSERVATIONS: The present study was carried out in patients having resistant hypertension admitted in medicine wards as well as in OPD patients at tertiary care hospital. Out of 40 patients, 7 (17.5%) were OPD (Outpatient department) & remaining 33 (82.5%) were IPD (Indoor patient department) patients. 29 were males and 11 were females.

Table-1: Causes of Resistant Hypertension

Cause	No. of cases	% of cases
CKD	17	42.5
CKD + RAS	1	2.5
CKD + CA	1	2.5
Essential HTN	15	37.5
RAS	4	10.0
SLE Nephropathy	2	5.0
Total	40	100.0

Table-2: Number of antihypertensive drugs patient receiving

No. of anti hypertensives	No. of cases	% of cases
3	14	35.0
4	24	60.0
5	2	5.0
Total	40	100.

Table-3: Antihypertensive Used.

Class of Drug	No. of cases	% of cases
Diuretics	40	100.0
CCB	35	87.5
BB	27	67.5
ARB	8	20.0
ACEI	6	15.0
AB	27	67.5
CS	4	10.0

Shows the distribution of patients according to the class of antihypertensive drug they were taking. All patients (n=40) were receiving diuretics as antihypertensive. Next most commonly used class of drug was calcium channel blockers (n=35, 87.5%), followed by Beta blockers and Alpha blockers in 27 patients (67.5%). Angiotensin receptor blockers (ARBs) were used in 8 patients (20%), Angiotensin converting enzyme inhibitors (ACEIs) were used in 6 patients (15%) and central sympatholytic were used in least number of patients (n= 4, 10%).

Summary and Conclusions : From the present study, we conclude that

- Resistant hypertension in more common in age between 41-50 years and it is more common in males.
- Most common risk factor was found to be Tobacco use which is followed by Smoking. Obesity as a risk factor was found in 9 patients according to Body mass index (BMI) and in 28 patients according to waist to hip ratio (WHR).
- Most common cause of resistant hypertension in this study was found to be Chronic kidney disease (CKD), followed by Essential hypertension.
- Majority of the patients were using 4 antihypertensive drugs. Most common used antihypertensives was Diuretics followed by calcium channel blockers.

Expanding our understanding of the causes of resistant hypertension and thereby potentially allowing for more effective prevention and / or treatment will be essential to improve the long-term clinical management of this disorder.

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