

Resistant Hypertension: Newer Management Approaches

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ABSTRACT

Hypertension is one of the most common condition seen in general clinical practice. Hypertension if not treated can lead to many serious complications such as stroke, myocardial infarction, renal failure and eventually death. The incidence of resistant hypertension defined as the inability to achieve target blood pressure despite optimal doses of 3 or more antihypertensive drugs, including one diuretic is increasing. Resistant hypertension further increases the risk of cardiovascular complications. The diagnosis of resistant hypertension is mainly by exclusion criteria. White coat syndrome and poor adherence to treatment should be excluded. Management involves multiple approaches such as lifestyle interventions and pharmacological treatment. Initial pharmacological treatment begins with optimization of diuretic use. Other first line drugs are calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers. Combination of other drugs is used as per individual patient need. Spironolactone has shown promising results in the management. Various device therapies like chronic electrical stimulation of the carotid sinus and Catheter-based renal sympathetic denervation have been tried in the management of resistant hypertension though the success is still eluding. The endothelin receptor antagonists and minodoxil are being evaluated in the management of resistant hypertension.

Keywords: Resistant hypertension, Diuretics, Calcium channel blockers, Angiotensin-converting enzyme inhibitors.

INTRODUCTION

Hypertension is considered to be one of the major preventable cause to disease and death.¹ Cardiovascular diseases are responsible for around 17 million deaths worldwide in a year.² Among these hypertension is responsible for 9.4 million

deaths.³ Various randomized controlled trials have shown antihypertensive drug treatment to have a beneficial effects in reducing health outcomes in people with hypertension.⁴⁻⁶ Resistant hypertension is commonly seen in clinical practice and the

incidence is increasing.⁷ Initially evaluation all resistant hypertension patients starts with assessing adherence to medications. The diagnosis of resistant hypertension is mainly by exclusion criteria. White coat hypertension should be ruled out. Resistant hypertension may be sometimes due to secondary causes like aldosteronism, renal disease, obstructive sleep apnea (temporary cessation of breathing during sleep) etc., patients must undergo screening for the above conditions.

Definition and prevalence

Resistant hypertension is defined as “The inability to achieve a blood pressure lower than 140/90 mm Hg despite optimal doses of 3 or more antihypertensive drugs, including one diuretic”⁸ by the seventh Joint National Committee (JNC 7). The American Heart Association defines resistant hypertension as “uncontrolled hypertension despite treatment with at least 3 antihypertensive drugs or controlled hypertension with at least 4 drugs.”⁸ In a Survey done in USA from the year 2005 to 2008, 13% of hypertensive patients were found to be case of resistant hypertension as per JNC 7 definition and it was 21% as per American Heart Association definition.⁷ Uncontrolled hypertension and resistant hypertension are not to be considered same. Uncontrolled hypertension includes all the patients who does not have adequate blood pressure control which may be either due to poor adherence or inadequate treatment regimen, in addition it also includes cases of true treatment resistance.⁹

Resistant hypertension

Contributing factors

There are multiple factors contributing to resistant hypertension. Patient characteristics including life style, genetic factors, various drugs used for other conditions all contribute to resistant

hypertension. The list of patient characteristics that contribute to resistant hypertension are given in table 1. Heavy alcohol consumption is associated with increased the risk to develop resistant hypertension. Higher salt intake is seen in most of the resistant hypertension patients when compared the general population, with daily dietary sodium consumption of more 10 grams.^{9,10} (See table 1.)

Genetic characteristics

Genetic study results are provocative. Liddle’s syndrome, which is a rare form of hypertension causes due mutations of the β and γ subunits of the epithelial sodium channel. In a genetic study it observed that compared to control group, resistant hypertensive patients had significantly more gene variants of β and γ sub units. In a study involving African-American patients it was seen that CYP3A5*1 allele was associated with resistant hypertension.¹⁰ (See table 2.)

Secondary causes of resistant hypertension

There are various secondary causes of resistant hypertension. Sleep apnea-temporary cessation of breathing during sleep, is seen in many patients with resistant hypertension, but the mechanism is poorly understood. Increase in reactive oxygen species with concomitant reductions in nitric oxide bioavailability is postulated to be the reason behind it. In sleep apnea, there is increased sympathetic nervous system activity due to intermittent hypoxia. Increase in sympathetic nervous system output lead to raise blood pressure by increasing cardiac output and peripheral resistance. It also leads to fluid retention, which adds up to the effect. Primary aldosteronism is also common in patients with resistant hypertension. Activation of renin-angiotensin-aldosterone system is believed to play a role in obesity. Certain secretagogues are released by adipocytes, these stimulate the release of aldosterone. Chronic kidney disease

is both a common cause and complication of poorly controlled hypertension. Chronic kidney disease treatment resistance, hypertension is due to increased sodium and fluid retention. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) concluded that chronic kidney disease is a strong predictor of treatment resistance, hypertension.^{9,10} (See table 3.)

Diagnosing resistant hypertension

Before diagnosing resistant hypertension Pseudo-resistance should be excluded. Pseudo-resistance means lack of adequate blood pressure control in spite of appropriate treatment in a patient who actually does not have resistant hypertension. The cause of pseudo-resistance include poor adherence to treatment and white coat syndrome. White coat hypertension is “defined as office blood pressure of 140/90mmHg or higher, but normal 24-hour ambulatory blood pressure of 130/80mmHg.”⁷ The prevalence of white coat hypertension is as high as 30%. Non adherence to antihypertensive medications is one of the major causes for pseudo resistant hypertension.^{9,10}

Management

Management involves multiple approaches such as lifestyle Interventions, pharmacological treatment and device therapy.

Lifestyle interventions

Weight loss

Weight loss, especially in obese patients has shown to reduce blood pressure and also a reduction in the number of prescribed medications. Weight loss of 10 kg is associated with an average 6.0-mm Hg reduction in systolic and a 4.6-mm Hg reduction in diastolic blood pressure.^{11,12} Obese patients should be educated about the

importance weight loss in the reduction of blood pressure.

Dietary salt restriction

From Meta-analyses, it was shown that sodium restriction to approximately 1.7g/d lead to reduction of blood pressure by 5/3 mm Hg. The effect was even more in resistant hypertension patients.¹³

Physical activity

Physical inactivity is seen in more than 40% of patients with resistant hypertension.¹⁴ Most of the guidelines advocate regular physical activity for patients with resistant hypertension.^{7,15} Physical activity should be encouraged in all the patients with resistant hypertension.

Pharmacotherapy

Initial pharmacological treatment of resistant hypertension begins with optimization of diuretic use. Chlorthalidone, a thiazide-type diuretic and indapamide are recommended by various committee.⁷ (See table 4.)

Once the dose of diuretics is optimized, a combination of calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors are prescribed. This combination is superior to the combination of ACE inhibitors and thiazide diuretics in reducing cardiovascular events in hypertensive patients with high cardiovascular risk.¹⁶ In a randomized clinical trial blood pressure was controlled in more than 60% of patients who received combination ACE inhibitors and calcium channel blockers, in whom previous therapy regimen had failed to achieve target blood pressure.⁷ The results of the studies suggest use of this combination is suitable in the initial management of resistant hypertension. ASPIRANT trail results showed a reduction in 24-hour ambulatory systolic blood pressure by 10mm Hg in

patients receiving spironolactone compared with placebo in patients with resistant hypertension as an add on to standard treatment regimen.¹⁷ A rapid regression of left ventricular hypertrophy was seen in the resistant hypertension patients in whom spironolactone was added.¹⁸ Various studies suggested the potential role of spironolactone and eplerenone in the management of resistant hypertension.¹⁷⁻²⁰ Eplerenone does not have the antiandrogenic adverse effects seen with spironolactone.²⁰ In the patients with primary aldosteronism α -Blockers can be used as an alternative to spironolactone because α -Blockers does not affect plasma renin activity and serum aldosterone level.²¹ In a clinical trial including two groups, one group receiving amlodipine plus perindopril and other group receiving atenolol plus bendroflumethiazide, addition of doxazosin to both groups was associated with a lower blood pressure.²² Secondary causes for resistant hypertension should be promptly evaluated and treated accordingly.

Device therapy

Various device therapies have been tried in the management of resistant hypertension. These devices target the sympathetic nervous system. There is an overwhelming evidence of involvement of sympathetic nervous system in the pathogenesis of secondary hypertension.²³ The complete success with device therapy is still eluding.

Chronic electrical stimulation of the carotid sinus

Chronic electrical stimuli are applied to carotid sinus nerves with a surgically implantable device. This triggers baroreflex-mediated inhibition of sympathetic nerve activity. Reduced blood pressure was seen in 54% of patients with resistant hypertension in a trial.²⁴

Catheter-based renal sympathetic denervation

This is a novel technique in which radiofrequency energy is used to ablate renal nerves alongside renal arteries.²⁵ Sham-controlled trial (SIMPLICITY-HTN3) showed that there was no difference in blood pressure in a denervation group as compared to a group who received only medicines.²⁶

Future therapies

The endothelin receptor antagonists are being evaluated as a therapeutic option in resistant hypertension. Darusentan, a selective endothelin receptor antagonist, is seen to be associated with BP reduction in patients with resistant hypertension in clinical studies.²⁷ Combination therapy of spironolactone with chlorthalidone are being evaluated. The addition of chlorthalidone decreases the sympathetic activity and supplement the effect of spironolactone.²⁸ Minodoxil is being evaluated in the management of resistant hypertension.²⁹

CONCLUSION

Treatment of resistant hypertension is a demanding and multidisciplinary task. Each patient should be evaluated properly to check for adherence before diagnosing as resistant hypertension. Additional drug selection should be tailor made to suit the individual patient. The cost of the treatment, cardiovascular benefits and adverse effects of the drugs should be considered before adding any new drug. Where ever secondary causes are identified it should be treated promptly. Patients with resistant hypertension require to take multiple drugs plus other additional drugs which may be prescribed for associated co morbidities. Therefore, patient education and proper counselling regarding to stick to the treatment regimen and follow a healthy lifestyle plays a significant role in the management of resistant hypertension.

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Table 1. Patient characteristics^{9,10}

Patient characteristics
Old age (>75 years)
High baseline blood pressure
Obesity (BMI- 30 kg/m ²)
Excessive dietary salt ingestion
Chronic kidney disease (serum creatinine of ≥1.5mg/dL)
Diabetes
Left ventricular hypertrophy
Black race
Female sex

Table 2. List of common drugs associated with resistant hypertension^{9,10}

Common drugs associated with resistant hypertension
Nonsteroidal anti-inflammatory agents (NSAIDs)
Sympathomimetic agents (decongestants, diet pills, cocaine)
amphetamine, methamphetamine, modafinil
Adrenal steroid hormones
Oral contraceptives
Cyclosporine and tacrolimus
Erythropoietin
Natural licorice (included in some chewing tobacco)
Herbal compounds (ephedra or ma huang)

Table 3. List of secondary causes of resistant hypertension^{9,10}

Secondary causes of resistant hypertension
Common
Obstructive sleep apnea
Renal parenchymal disease
Primary aldosteronism
Renal artery stenosis
Uncommon
Pheochromocytoma
Cushing's disease
Hyperparathyroidism
Aortic coarctation
Intracranial tumor

Table 4. List of drugs used in the treatment of resistant hypertension⁷

Pharmacological treatment
First-line drugs: 3-drug treatment with diuretic therapy for resistant hypertension
Diuretics
Calcium channel blockers
Angiotensin-converting enzyme inhibitors
Angiotensin-receptor blockers
Fourth-line drug therapy
Mineralocorticoid receptor antagonists
Fifth-line drug therapy
Direct renin inhibitors
β-Blockers
α-Blockers
Central sympatholytics
Direct vasodilators