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Review Article

Recapitulating the Management of Hypertension

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Abstract

Introduction: Every year, approximately 2 million new cases of hypertension are diagnosed. On a worldwide scale, approximately 1 billion people are hypertensive, and it is projected to reach a mark of 1.56 billion by the end of 2025. Hypertension is the most prominent reason for death and the second most common reason for disability-adjusted life. Hypertension is the leading cause of strokes, including cerebral and subarachnoid hemorrhage, heart diseases, kidney-related diseases, and macrovascular diseases. A good understanding of lifestyle modifications and the usage of pharmacological agents in a supervised manner can help reduce hypertension and let the patients achieve an appropriate blood pressure goal. Hypertension is the number one modifiable risk factor that can be easily controlled through lifestyle modifications and pharmacological options reducing the life-threatening complications associated with it.

Aim of Work: The present study aims to review the management of hypertension.

Methodology: The review is a comprehensive research of PUBMED and Google scholar from the year 1999 to 2022.

Conclusion: Hypertension is a modifiable global epidemic. If not treated at the right time, hypertension can lead to many risk factors leading to morbidity and mortality. The first step in hypertension management should be lifestyle modification which has proven to reduce blood pressure values to a great extent. Most patients require a pharmacological intervention which should be initiated at the initial stage to increase efficiency and reduce side effects. Monotherapy might not be sufficient for some patients, and they require a combination of drugs to control hypertension. A thorough management technique for hypertension includes a good screening, initiation of the pharmacological and non-pharmacological treatment plan at the right time, good communication between the patient and the healthcare worker, and good patient compliance.

Keywords: *Hypertension; Diuretics; DASH Diet; Vasodilator; Beta-Blockers*

Introduction

Every year approximately 2 million new cases of hypertension are diagnosed [1]. In a study based on the US population, it was seen that approximately 28% of the population was prehypertensive, and 7% were unaware of their hypertension status. On a worldwide scale, approximately 1 billion people are hypertensive, and it is projected to reach a mark of 1.56 billion by the end of 2025 [2]. Hypertension is the most prominent reason for death and the second most common reason for disability-adjusted life [2]. Hypertension is the leading cause of strokes, including cerebral and subarachnoid hemorrhage, heart diseases, kidney-related diseases, and macrovascular diseases [3].

Antihypertensive medications constitute approximately 10% of the total annual drug expenditure in the United States, with the total cost, including direct and indirect costs summing up to 73 billion dollars in the year 2009. Even after this expenditure, around 60% of the American population is not near its targeted blood pressure value [4].

The main reason for this failure to achieve the targeted blood pressure values is the multifactorial etiology and treatment planning. A good understanding of lifestyle modifications and the usage of pharmacological agents in a supervised manner can help reduce hypertension and let the patients achieve an appropriate blood pressure goal. Hypertension is the number one modifiable risk factor that can be easily controlled through lifestyle modifications and pharmacological options reducing the life-threatening complications associated with it [1].

Screening and diagnosis

All adults older than 18 years should be screened for hypertension. The frequency of screening may vary according to the blood pressure value of the patients. For patients with BP lower than 120/80 mm Hg, screening should be done every two years, and a BP reading of 120-140/80-90 mm hg comes under screening every year [2]. The blood pressure readings of the patients should always be correlated to the medical and physical examination of the patient. Patients suspected of "white coat" hypertension, where the patient's bp value increases in a medical setup or in front of a physician and is normal outside of such an environment, should be measured at their house, or ambulatory BP monitoring should be considered in their case. To classify a patient as hypertensive, at least two readings of bp measuring more than 140/90 mm Hg divided amongst 3 - 4 visits within a span of 2 - 3 weeks should be taken into account. The blood pressure value should also be correlated with the lab findings like a complete hemogram, kidney, and liver function tests, basic metabolic panel, and electrocardiogram [5].

In patients with any reversible precipitating factors. The most important goal of blood pressure evaluation and hypertension diagnosis is to look for any end organ damage and any additional cardiovascular risk factor [6].

Management techniques

The targeted goal for the blood pressure values differs from patient to patient according to their present ailment. The targeted BP value should be less than 140/90, but in patients with diabetes and renal diseases, the goal reduces to 130/80 mm Hg. Apart from pharmacological interventions, lifestyle modification also helps in reducing hypertension. Lifestyle modification helps in the initial management of hypertension and reduces the risks of complications associated with it. However, in the long run, most patients have to resort to a pharmacological treatment plan to control their blood pressure values [1].

Non-pharmacological management of hypertension

1. **Diet modification:** Reduction of blood pressure values can be achieved by following a diet enriched with fruits, vegetables, fish, legumes, etc. avoiding saturated fats and red meat, and reduction in the overall sugar intake. The research on the Dietary approach to stop hypertension (DASH) revealed that by following a diet high in vegetables and fruits and reduced red meat, sweetened beverages, and refined dairy products, a reduction of 5.5 mm Hg in systolic and 3 mm Hg in diastolic blood pressure is seen [7]. The DASH diet focuses on lowering the sodium intake, which in turn reduces the blood pressure value. Another dietary modification that can be adapted is inculcating the intermittent fasting approach, which helps in reducing the markers of inflammation like interleukin 6, CRP and homocysteine, which stops the formation of atherosclerotic plaques resulting in lowered BP values [8].

2. **Increased physical activity and weight loss:** A minimum duration of 150 minutes of exercise a week has been shown to help to reduce blood pressure levels and alleviate other health issues like breast cancer, colon cancer, type 2 diabetes, and coronary heart disease [9].

Table 1 enumerates the various non-pharmacological methods to reduce hypertension and the degree to which the reduction has been seen [10].

Non-pharmacological treatment approach	Levels of blood pressure value reduction
1. Diet modification (DASH diet)	SBP - 5 mm Hg DBP - 3 mm Hg
2. Reduction in sodium intake	SBP - 7 mmHg DBP - 3 mm Hg
3. Reduction in Potassium intake	SBP - 6.8 mm Hg DBP - 4.6 mm Hg
4. Increase in magnesium intake	SBP - 2 mm Hg DBP - 1.78 mm Hg
5. Reduction in alcohol consumption	SBP - 5 mm Hg DBP - 3 mm Hg
6. Body Weight Reduction	5 - 20 mm Hg
7. Transcendental meditation	Men- SBP - 12.7 mm Hg Women- SBP - 10.4 mm Hg DBP - 8.1 mm Hg DBP - 5.9 mm Hg
8. Regular monitoring of blood pressure at home	2.1 to 8.3 mm Hg

Table 1: *Reduction of blood pressure values following non-pharmacological treatment methods [10].*

Pharmacological management of hypertension

Lifestyle modifications need a great level of patient compliance. In some cases, if the patient is not complying with the lifestyle modifications or if, even after the lifestyle modifications, targeted bp values are not able to be achieved, a pharmacological treatment option is the best management technique that can be applied. Diuretics, angiotensin-converting enzymes (ACE) inhibitors, calcium channel blockers (CCB), beta-blockers, and angiotensin receptor blockers (ARB) are used as the first line of treatment for hypertensive patients. According to the targeted bp values, some patients might need a combination of 2 or more antihypertensive drugs, which can be combined, keeping in mind their mechanism of action which should be complimenting the other. Antihypertensive drugs may also show some side effects, and hence while administering combination therapy, the second drug used should counter the side effects of the first one [11].

Diuretics

Thiazides, loop, and potassium-sparing diuretics are the various diuretic agents used to regulate blood pressure values. The mechanism of action for thiazides is the inhibition of sodium and chloride absorption in the distal convoluted tubule. In the 1990s, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [11] proved the efficiency of thiazides for heart failure, coronary artery disease, and stroke. This trial then led to JNC-7 declaring thiazides as the first line of treatment for hypertension. Considering the efficiency and lower price, the preferred thiazide agent by clinicians has been narrowed down to chlorthalidone [12].

The mechanism of action of food loop diuretics is the reduction in sodium chloride reabsorption in the ascending loop of Henle. Patients with congestive heart failure, pulmonary edema, and renal disease are preferably prescribed loop diuretics [13]. Potassium-sparing diuretics are generally used in conjunction with other antihypertensive drugs as they are mild diuretics. They act on the distal and cortical collecting tubules to reduce sodium reabsorption. In order to reduce the hyperkalemic effects of potassium-sparing diuretics, they should be used with caution when administered with ARB and ACE inhibitors [14].

Angiotensin converting enzyme inhibitors

ACE inhibitors stop angiotensin I from converting into active angiotensin II and increase the number of bradykinins and prostaglandins in order to reduce blood pressure values. Patients with a high risk of coronary artery disease, stroke, heart failure, myocardial infarction, kidney disease, and diabetes are generally prescribed ACE inhibitors as the first line of the drug. Durham Veterans Affairs Medical Center (VAMC) conducted a study that revealed that ACE inhibitors have a better cost efficiency and hence should be given a preference over ARB for the initial management of hypertension [15].

Angiotensin receptor blockers

ARBs help in the prevention of vasoconstriction and fluid retention by blocking angiotensin II from binding to their receptors. In a trial comparing telmisartan and ACE inhibitors in patients with no history of heart failure, it was seen that telmisartan was as effective as any ace inhibitors in the reduction of cardiovascular and renal events. Cochrane research held in 2008 showed comparable efficiency of ACE inhibitors and ARBs in blood pressure reduction. The main drawback of ARBs is the cost factor. As mentioned earlier in this article, ARBs have shown to be less cost-effective when compared to ACE inhibitors and hence are suggested to be used only in case of any known allergies or failure to ACE inhibitors [16].

Renin-inhibitors

Aliskiren is used as a second line of drugs in the management of hypertension. It utilizes renin inhibition to stop the conversion of angiotensinogen to angiotensin I. The preferred group of patients for aliskiren are diabetic patients because of its renoprotective effects, as it reduces the urinary albumin to creatinine ratio by 20%. Aliskiren, when compared to ramipril, has shown better results in reducing

SBP, and even better results are seen when it is used in combination therapy. The main drawback of renin inhibitors is the cost efficiency and a lesser research base in comparison to ARBs and ACE inhibitors, making it the second line of the drug [17].

Calcium channel blockers (CCB)

BP reduction by CCBs is through vasodilation and reduced vascular contraction. Dihydropyridines and non-dihydropyridines are the two types of CCBs that act on peripheral blood vessels and cardiac muscles along with peripheral blood vessels, respectively. Elderly patients and patients with cardiovascular events and strokes have shown good results with dihydropyridines. Patients with cardiac arrhythmias have shown better results with non-dihydropyridines. Even when used in monotherapy, both dihydropyridines and non-dihydropyridines have given good results. When administered in combination with ACE inhibitors, CCBs have shown good results. Patients with cardiovascular disease and diabetes have shown good results with CCBs as the first line of the drug as recognized by JNC-7 [18].

Table 2 summarizes the various antihypertensive agents with common drugs being used in daily life [19].

Class of drugs used	Common examples and dosage	Common side effects
1. ACE inhibitors	1. Benazepril (10 - 40 mg/d) 2. Captopril (25 - 100 mg/d) 3. Enalapril (2.5 - 40 mg/d) 4. Fosinopril (10 - 40 mg/d) 5. Lisinopril (5 - 40 mg/d) 6. Ramipril (1.25 - 20 mg/d) 7. Moexipril (7.5 - 30 mg/d) 8. Perindopril (4 - 16 mg/d)	Reduced BP value, rashes and loss of taste have been seen with captopril, cough, headache.
2. ARB	1. Candesartan (8 - 32 mg/d) 2. Losartan (25 - 100 mg/d) 3. Olmesartan (20 - 40 mg/d) 4. Irbesartan (75 - 300 mg/d) 5. Telmisartan (20 - 80 mg/d)	Hyperkalemia dizziness, fatigue, diarrhea
3. Calcium channel blockers	a. Dihydropyridines 1. Amlodipine (2.5 - 10 mg/d) 2. Felodipine (2.5 - 20 mg/d) 3. Nifedipine (30 - 60 mg/d) b. Nondihydropyridines 1. Diltiazem (120 - 420 mg/d) 2. Verapamil (120 - 480 mg/d)	Peripheral edema, palpitations, headache Weakness, increased heart rate, reduced blood pressure, dizziness.
4. Diuretics	a. Loop Diuretics 1. Bumetanide (0.5 - 2 mg/d) 2. Furosemide (20 - 80 mg/d) 3. Torsemide (2.5 - 10 mg/d) b. Thiazide 1. Chlorthalidone (12.5 - 25 mg/d) 2. Hydrochlorothiazide (12.5 - 50 mg/d) 3. Indapamide (1.25 - 2.5 mg/d) 4. Metolazone (1.25 - 5 mg/d) c. Potassium sparing diuretics 1. Amiloride (5 - 10 mg/d) 2. Triamterene (50 - 100 mg/d)	Increased frequency of urination, reduced potassium levels, increased readings of uric acid in the blood. Increased calcium levels seen in loop diuretics which is absent in other diuretics. Weakness, headache and dizziness is also seen.

5. Beta blockers	1. Atenolol (25 - 100 mg/d) 2. Bisoprolol (2.5 - 10 mg/d) 3. Labetalol (200 - 800 mg/d) 4. Metoprolol Tartrate (50 - 100 mg/d) 5. Propranolol (40 - 160 mg/d)	Disturbed sleep. Decreased heart rate, gastrointestinal disturbances, asthma, peripheral circulation is reduced. Dizziness and fatigue also seen.
6. Alpha blockers	a. Alpha 1 blockers 1. Doxazosin (1 - 16 mg/d) 2. Prazosin (2 - 10 mg/d) b. Alpha 2 blockers 1. Clonidine (0.1 - 0.8 mg/d) 2. Methyldopa (250 - 1000 mg/d)	Decreased energy, orthostatic hypotension, palpitations.
7. Direct Vasodilators	1. Hydralazine (25 - 100 mg/d) 2. Minoxidil (2.5 - 80 mg/d)	Water retention and increased hair growth even in women seen with minoxidil.
8. Aldosterone antagonists	1. Eplerenone (50 - 100 mg/d) 2. Spironolactone (25 - 50 mg/d)	Gastrointestinal disturbance, dizziness, increased potassium levels, disturbances in the menstrual cycle.

Table 2: *Various oral hypertension medications and associated side effects [19].*

Beta-blockers

Beta-blockers reduce cardiac contractility and cardiac output and slow down the heart rate as a result of blocking beta-1 adrenergic receptors, thereby reducing blood pressure. Patients with asymptomatic left ventricular hypertrophy and congestive heart failure also benefit from renin inhibition and angiotensin II production [20]. Beta-1 receptors are present primarily in the heart, and beta-2 receptors are seen in the lungs, kidneys, and blood vessels. When selecting beta blockers, we have to keep in mind receptor selectivity and sympathomimetic activity. Atenolol, bisoprolol, and metoprolol are considered cardioselective blockers as they have a greater affinity towards beta-1 receptors. BP lowering ability of some beta blockers arises because they block the alpha receptors. Pindolol shows intrinsic sympathomimetic activity and hence can be administered in cases of decreased heart rate. In older patients (age > 60), beta-blockers are used cautiously and are not the preferred agent because of the higher risk of mortality and stroke associated with it. Patients with underlying cardiac issues are generally administered beta blockers, but in the absence of any underlying cardiac issues, beta blockers are not considered the first line of the drug. When compared with other antihypertensive drugs, beta-blockers have shown a decreased ability to lower blood pressure values [21]. In a 200 Cochrane review, beta-blockers were seen not giving results as effective as calcium channel blockers, diuretics, ARB, and ACE inhibitors and hence could not be used as the first line of drug for hypertensive patients [22].

Alpha-blockers have a very limited use case and can be administered to men with benign prostatic hypertrophy. Alpha-blockers act on the vascular smooth muscles and block the alpha-1 adrenoreceptors. When compared with chlorthalidone, it has shown an increased risk of cardiovascular events [23].

Direct vasodilators

As the name suggests, vasodilators directly act on vascular smooth muscles and have a relaxing effect on them. Minoxidil and Hydralazine are the common agents in this class. Vasodilators are generally used as an add-on medication in combination therapies as the side effects reported by them have been higher. The main indication for vasodilator usage in patients with renal insufficiency and combination drugs in patients with severe hypertension. Vasodilators, when used with beta-blockers or diuretics, help in decreasing the tachycardia and fluid retention associated with them. Minoxidil can also be used once a day for patients with hair loss, as it has been seen to cause

diffuse hair growth both in men and women. Reversible systemic lupus erythematosus has been recorded in patients on Hydralazine. The usage of vasodilators is hence done cautiously and mostly in combination with other drugs [19].

Figure 1 shows the flow of hypertension management step by step, considering the patient's systemic conditions and severity of hypertension [19].

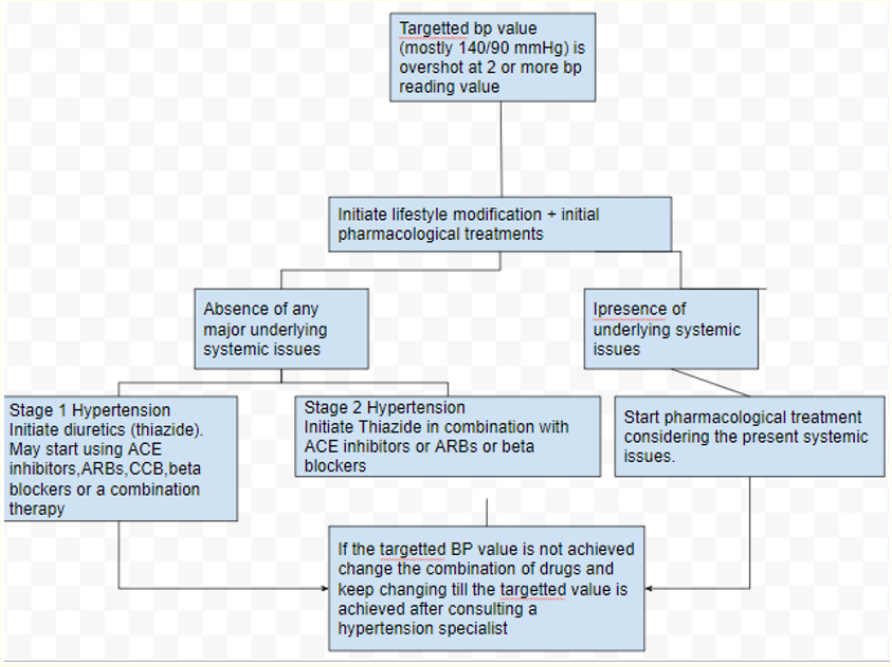

Figure 1: *Treatment flow for hypertension management [19].*

Combination therapy in hypertension management

Combination therapy refers to the use of 2 or more antihypertensive drugs which have a complementary mechanism of action and help in negating the side effects of the other drug. When the blood pressure value of the patients is above 20/10 mm Hg more than the targeted blood pressure, it indicates that monotherapy is not sufficient, and the patient is put on a combination treatment regimen for hypertension management. Combination therapy has been shown to give a faster response at a lower cost and lesser side effects. In the initial management of hypertension, the combination of ACE inhibitors or ARB with a diuretic has shown a good response. In the ONTARGET study, it was seen that the combination of ACE inhibitors with ARB was not a preferable choice and the side effects like renal dysfunction, hypotension, and syncope increased by a great margin. The combination of ACE inhibitors or ARB with a calcium channel blocker has proven to be a very effective combination [24].

Conclusion

Hypertension is a modifiable global epidemic. If not treated at the right time, hypertension can lead to many risk factors leading to morbidity and mortality. The first step in hypertension management should be lifestyle modification which has proven to reduce blood

pressure values to a great extent. A balanced diet, meditation, and exercise are various modifications that help control blood pressure values. Most patients require pharmacological intervention, and it should be initiated at the initial stage to increase efficiency and reduce side effects. Monotherapy might not be sufficient for some patients, and they require a combination of drugs to control hypertension. The main aim of hypertension management is to achieve the BP goal of the patient considering their other underlying systemic issues. A thorough management technique for hypertension includes a good screening, initiation of the pharmacological and non-pharmacological treatment plan at the right time, good communication between the patient and the healthcare worker, and good patient compliance.

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