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Open Access Review Article

Management of Hypertension with Conventional and Herbals Drugs

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ABSTRACT

In this article, we have discussed about Types (primary, secondary, isolated, white coat, malignant, resistant and pulmonary hypertension), classification, adverse drug reactions of antihypertensive drugs (beta-blocker induce psoriasis and calcium channel blocker cause peripheral oedema. ACE inhibitor produce ankle oedema and thiazide diuretics causes hypenatremia and also hyperglycaemia. These are some of the serious adverse drug reactions associated with patients who are being treated with these drugs), measurement, management, diagnosis and associated diseases (e.g. diabetes mellitus, heart disease, cerebrovascular disease) lastly concluded about the herbal approach for management of hypertension .

Keywords: Hypertension, conventional drugs, Herbal drugs

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1. INTRODUCTION

Persistent elevation in blood pressure is known as hypertension. In hypertension, systolic blood pressure (SBP) is greater than 140 mmHg or diastolic blood pressure (DBP) is greater than 90 mmHg.[14]

Table 1: Categories/stages of hypertension: (14)

Category	SBP	DBP
Normal	<120	<80
Pre-hypertension	120-139	80-89
Stage-1	140-159	90-99
Stage-2	>160	>100

Blood pressure (BP) = cardiac output (CO) × peripheral vascular resistance

Cardiac output (CO) = heart rate (H.R.) × stroke volume (SV)

Heart rate: number of beats per minute (72).

Stroke volume: The amount of blood pumped in 1 heart beat (60ml).

1.1 Epidemiology

Hypertension is public health problem in both developing and developed countries and affecting about 20% adult population shown in figure 1. Worldwide, 7.5 million premature deaths (about 13.5% of the global total) were due to hypertension. About 55% of stroke and 48% of ischaemic heart diseases worldwide attributable to high blood pressure. Prevalence of hypertension in India is about 27% in men and 24% in women. According to statistics cases of hypertension increased 10 times in last 4 decades in rural India and almost 30 times in urban India [1].

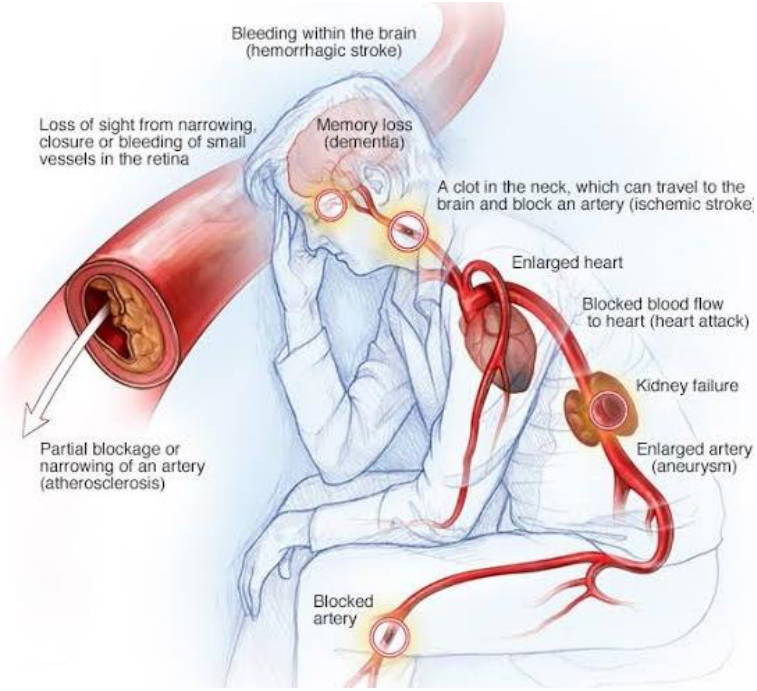

Fig. 1 Negative impact of hypertension

1.2 Symptoms

Hypertension has no sign and symptoms. Therefore, it is also called as **"silent killer".** A small amount of people may experience symptoms such as:

- Severe Headache
- Vomiting
- Nosebleeds
- Fatigue
- Chest pain
- Blurred vision

But, these symptoms usually do not occur until blood pressure level reaches to life threatening stage [2].

1.3 Causes of Hypertension

- Hereditary
- Obesity
- High sodium intake
- Psychological stress
- stress

Other factors also play a role:

- Excessive alcohol drinking
- Smoking
- Physical inactivity [3].

2. TYPES OF HYPERTENSION

2.1 Primary hypertension/essential hypertension (95 to 96%): it has no clear cause. But, frequent headache and tiredness is common.

2.2 Secondary hypertension (4 to 5%): in secondary hypertension cause can be found and it includes:

- Hormonal abnormalities
- Too much salt in the diet
- Alcohol consumption
- Drugs can also cause secondary hypertension

Example: over the counter drug (OTC), ibuprofen, Pseudoephedrine.

If the cause is found, hypertension (HTN) can often be controlled [4].

3. OTHER TYPES OF HYPERTENSION

3.1 Isolated systolic hypertension: in this, systolic blood pressure tends to rise above 140 and diastolic blood pressure tends to fall and most common in people over the age 65.

3.2 White coat hypertension: this term is used to denote individuals who have normal BP outside doctor's office but, high BP in the medical environment therefore, the patients with this type of hypertension feel extremely stressed when they visit doctor's office.

3.3 Malignant hypertension: occur only in 1% of people with hypertension and in this DBP goes over 130, treated only in hospital.

3.4 Resistant hypertension: if three different types of medications are prescribed by the doctor but, blood pressure is still too high. Then it is called resistant hypertension [5].

3.5 Pulmonary hypertension: pulmonary hypertension means high blood pressure in the arteries going to lung. In healthy individuals, the BP in these arteries is much lower than in the rest of the body.

Pulmonary arterial BP is about 25/10mmHg in healthy individuals. If this pressure exceeds 40/20 mmHg it means pulmonary hypertension is present [6].

4. CLASSIFICATION OF ANTI-HYPERTENSIVE DRUGS

4.1 Diuretics

Diuretics such as hydrochlorthiazide lower BP by increasing sodium and water excretion or urination. This cause a decrease in cardiac output and peripheral resistance and ultimately blood pressure decreases. Examples are Bumetanide, Furosemide, Hydrochlorthiazide, Spironolactone, Triamterene [14].

4.2 Beta-blockers

The β-blockers reduce blood pressure by decreasing cardiac output and also inhibit the release of rennin from the kidneys, thus decreasing the formation of angiotensin-2 and the secretion of aldosterone therefore volume of blood decreases which leads to decrease in BP. Examples are Atenolol, Propranolol, Labetolol, Timolol [14].

4.3 ACE inhibitors

These drug blocks the ACE that convert angiotensin-1 into angiotensin-2. Thus, ACE inhibitors decrease angiotensin-2 level so, reduce constriction and also secretion of aldosterone that control the level of sodium and water ions. Hence, B.P. decreases. Examples are Captopril, Enalapril, Lisinopril, Quinapril, Ramipril [14].

4.4 Angiotensin2-receptor antagonist (ARB)

Angiotensin receptor blocker alternative to the ACE inhibitors. These drugs blocks the AT1 receptors, result in vasodilatation and also block aldosterone secretion. Examples are Candesartan, Irbesartan, Losartan, Telmisartan, Valsartan [14].

4.5 Renin inhibitors

Aliskiren directly inhibit rennin and thus, acts earlier in the rennin angiotensin aldosterone system than ACE inhibitors or ARBs. It decreass blood pressure about as effectively as ARBs, ACE inhibitors and thiazides. For example Aliskiren. But, aliskiren cause diarrhea at higher doses [14].

4.6 Calcium channel blockers

Calcium is responsible for contraction and the calcium channel antagonist block the inward movement of calcium by binding to L-type calcium channels in the heart, these cause vascular smooth muscles to relax or channel blockers lower B.P by reducing myocardial contractility. For example, Amlodipinem, Diltiazem, Felodipine, Nicardipine, Nifedipine, Verapamil [14].

4.7 Alpha- blockers

Alpha blockers block the α1 receptor. They decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscles because these receptors are present on vascular smooth muscle. For example Prazosin, Doxazosin [14].

4.8 Other

Sodium nitroprusside: nitroprusside is administered intravenously and cause prompt vasodilation. It is capable of reducing BP in all the patients.but, nitroprusside is metabolized quickly and requires continuous infusion for the maintainance of its hypotensive action. For example Hydralazine(vasodilator) [14].

Table 2: Commonly used antihypertensive drugs: [7].

S.NO.	CLASS	GENERIC NAME	DOSE(mg)	BRAND NAME
1.	Diuretics	Hydrochlorthiazide Indapamide furosemide	12.5-50 1.25-5 200-400	Hydrex Natrilex Lasix
2.	Beta-blocker	Atenolol Metaprolol	25-100 50-200	Blockium Betaloc
3.	Calcium antagonist	Verapamil Diltiazem	120-480 90-240	Tarka isoptin retard Tildium altiazem
4.	ACE inhibitors	Captopril Enalapril Lisinopril	50-150 2.5-40 10-40	Capozide Ezapril Zestril
5.	ARB	Losartan Valsartan Candesartan	25-100 80-320 4-32	Fortzar Co-diovan Atacand
6.	Alpha-blocker	Prazosin Doxazosin	1-16 1-16	Minipress Cardura
7.	Centrally acting drugs	Methyldopa Clonidine	500-2000 0.1-1.2	Aldomet Catapres

5. ADVERSE EFFECTS OF ANTI HYPERTENSIVE DRUGS

5.1 Hypokalemia

Diuretics cause hypokalemia and it is treated by rational medication combination. Low dose thiazide combined with ACE or ARBs to maintain the potassium concentration sufficiently.

5.2 Hyponatremia

One of the most common problems with thiazide diuretics is hyponatremia. Those who develop hyponatremia should be changed to other class of drugs. If still diuretics are required a low dose of long acting loop diuretics (e.g. torsemide 2.5-5mg daily) is effective.

5.3 Edema

Antihypertensive medication induced edema is more common. Women may be particularly susceptible to calcium channel blocker induced edema. But, peripheral edema can be minimized by decreasing the dose.

5.4 Erectile dysfunction

It affects about 30% of men with hypertension. Both hypertension and erectile dysfunction are disorders of endothelial dysfunction. Preliminary evidence suggests that combination of phosphodiesterase type-5 inhibitors (PDE5) and alpha-blockers improve erectile dysfunction [8].

5.5 Psoriasis

The use of beta-blocker may result in psoriasis and if we substitute any other beta-blocker it may further cause skin lesions. If psoriasis is present only in localized area then, emollients can be helpful.

5.6 Hyperglycaemia

Hyperglycaemia is more common and severe adverse effect is seen with thiazide diuretics than other class of anti-hypertensive drugs. Patient with diuretic induced hyperglycaemia are often considered as having type-2 diabetes and are prescribed with oral anti-diabetic agent [9].

6. B.P. MEASUREMENT

6.1 Sphygmomanometer

The sphygmomanometer was invented by **Samuel Siegfried Karl Ritter Von Basch** in the year 1881. Sphygmomanometer self-measurement of blood pressure device.

6.2 Points to be considered during the measurement of B.P. [10].

6.2.1 Posture of patient

Allow the patient to be seated for few minutes before the measurement of blood pressure. B.P. should be measured when the patient in a relaxed state, the arm at the level of heart and the legs are not crossed.

6.2.2 B.P. device

The device should be validated.

6.2.3 Cuff size

The cough with bladder whose length is at least 80% of the arm circumference is preferable.

6.2.4 Number of measurements

At least two readings should be taken at each visit with an interval of at least 1 min. this will avoid the calculation error involved in averaging the two measurements. Due to variability of B.P. measurements the diagnosis of hypertension should be made only after multiple readings.

Table 3:

S.NO.	Measurement error	Effect on B.P.
1.	Back is not supported	Diastolic blood pressure increased by 6mmHg
2.	Legs are crossed	Systolic B.P. increased by 2-8mmHg
3.	Arm is not at the level of heart	Increase B.P. by 10-12mmHg

7. MANAGEMENT OF HYPERTENSION [11].

Non pharmacological management plays an important role for the improvement of overall cardiovascular diseases. It include:

7.1 Weight reduction: Dietary interventions to lower body weight also recommended for people with hypertension. Weight reducing diet reduces about 4.5/3.2mmHg blood pressure.

7.2 Sodium intake: Reduce sodium intake sufficiently reduces B.P. in adults. A recent study has shown that reduction of sodium intake from 11.6g of salt to 3.8g of salt decrease the B.P. in asian people.

7.3 Alcohol consumption: Alcohol consumption increases B.P. reducing alcohol intake reduce B.P. by 3.3/2mmHg. People who drink are advised to limit the consumption of alcohol.

7.4 Regular physical activity: Increased physical activity has been shown to reduce blood pressure. Aerobic exercise of at least 150 min. per week is beneficial.

7.5 Healthy eating: A diet rich in fruits, vegetables, low fat dairy products can lower B.P. DASH (dietary approaches to stop hypertension) diet significantly lower the B.P. and it include, Grains, Vegetables, Fruits, Low fat dairy foods, Nut, seeds, beans.

7.6 Cessation of smoking: Smoking cessation is important in reducing global cardiovascular risk.

7.7 Dietary potassium intake: Increase dietary potassium intake reduces B.P. in adults without adverse effect on blood lipid concentration. Dietary potassium can reduce B.P. by 3.49/1.96mmHg and also lower the risk of stroke by 25% this can be achieved by eating fruits, vegetables, nuts and legumes.

8. ASSOCIATED DISEASES WITH HYPERTENSION

8.1 Diabetes mellitus

Patient with diabetes mellitus should be initiated on drug therapy when the SBP is greater than 140mmHg. ACE inhibitors are used initially than calcium channel blockers and diuretics used as add on therapy.

8.2 Heart disease

Beta-blockers used in patient with hypertension and a recent myocardial infarction. In case of angina, beta-blockers and calcium channel blockers are prefer but, in patient with heart failure and hypertension thiazide diuretics are more preferable.

8.3 Cerebrovascular disease

Initiation of drug treatment should be considered with grade 1 hypertension in patient with stroke history. Do not administer antihypertensive drugs in first 72 hours of ischemic stroke [12].

9. DIAGNOSIS OF HYPERTENSION:

9.1 Measure B.P. in both the arms for the diagnosis of hypertension

9.1.1 Repeat the measurements, if the difference in readings between arms is more than 15mmHg.

9.1.2 Measure subsequent B.P. in the arm if the difference between the arms more than 15mmHg on the second measurement.

9.2 When B.P. measurement is inside the clinic 140/90mmHg or higher

9.2.1 During the consultation take second measurement.

9.2.2 Take third measurement if second is different from first

9.3 Ambulatory blood pressure monitoring (ABPM) – if clinic blood pressure is between 140/90 and 180/120mmHg to confirm the diagnosis of hypertension.

9.4 If ABPM is unsuitable for the person offer home blood pressure monitoring (HBPM) for the diagnosis of hypertension.

9.5 When using ABPM ensure that at least 2 measurements taken per hour during the person's waking hour (e.g. between 8.00 and 22.00). When using HBPM ensure that for each blood pressure recording, 2 consecutive measurements are taken [13].

Patient presentation	Patient presents with uncontrolled BP (>140/90)
Check clinic blood pressure	Controlled clinic blood pressure measurement: Take a first measurement. Take a second measurement, if BP is high. If the last measurement is different from the first, take a third measurement. The last two measurements recorded as a clinic BP.
Rule out white coat hypertension	Refer for ambulatory BP monitoring, if blood pressure is uncontrolled.
Rule out non-adherence to medication	If BP is uncontrolled on ABPM consider: Urine analysis Directly observed dosing
Diagnosis	Diagnosis of resistant hypertension can be made if BP is uncontrolled.

10. NOVEL DRUG DELIVERY SYSTEM FOR HYPERTENSION

S. N.	Drug	Delivery system/formulation approaches	Applications
1.	Perindopril	Mucosal administration route ODT: orodispersible tablets perindopril arginine	Treatment of hypertension/heart failure[15].
2.	Nitrendipine	Sublingual mucosal route	Effectively reduce B.P during first 45 min[15].
3.	Amlodipine	Transmucosal administration	Effective in coronary heart disease and hypertension[15].
4.	Metaprolol	Rectal administration of metaprolol tartrate	Reduce B.P. significantly faster without severe side-effects[15].
5.	Propranolol	Rectal administration and Sublingual administation	Sustain release of drug[15].
6.	Carvedilol	Solid lipid nanoparticles(SLN) And nanosuspensions	Enhance bioavailability and protecting it from acidic environment[16].
7.	Candesartan cilexitil	Dendrimers and Nanosuspensions	Improved water solubility[16].
8.	Nifedipine	Polymeric nanoparticles and Dendrimers	Increase dissolution rate[16].
9.	Felodipine	Nanosuspensions/ Polymeric nanoparticles	Control the release of drug[16].
10.	Valsartan	Proliposomes and self non –emulsifying drug delivery system	*Bypass first pass metabolism *Prolong release of drug[16].
11.	Nebivolol	Polymeric nanoparticles	Prolonged drug release[16].
12.	Isradipine	Transdermal penetration of drug	Management of hypertension[17].
13.	Olmesartan	Nano-invasomes formulation/Transdermal delivery system(TDDS)	Increase bioavailability[17].
14.	Bosentan	Nanoparticles endothelin receptor antagonist	Effective in pulmonary hypertension[18].
15.	Aliskiren	Poly(D,L-lactide)(PLA) Oral gavage	Prevent stroke by lowering high B.P[18].
16.	Lacidipine	Niosomes	Helps to relax blood vessels[18].

17.	Captopril	Chitosan polymer/oral route	Improve survival after a heart attack
18.	Sildenafil	Endotracheal administration	Treat pulmonary hypertension[18].
19.	Tacrolimus(TAC)	Nanocompositae particles Endotracheal administration	Pulmonary hypertension
20.	Silaenafil	Poly (D,L-lactide-co-glycolide) nanoparticles Endotracheal administration	Pulmonary HTN[18].
21.	Cerivastatin	Liposomes Endotracheal administration	Pulmonary HTN[18].
22.	Lercanidipine	Proliposomes/ Oral dose using intragastric tube	Immediate and long lasting (24h) reduction in systolic blood pressure[19].
23.	Super- oxide dismutase (SOD)	Lipose encapsulation/daily injections	Reduce mean arterial pressure (MAP) by 50mmHg[19].
24.	Covera-HS;XL tablet	Osmotic control release oral drug delivery system(OROS)/ chronopharmaceuticals	Prevent the dangerous surge of B.P in the early morning[20].
25.	Verelan PM;XL release capsule	Chronotherapeutic oral drug absorption system(CODAS)	Manage hypertension in the morning[20].
26.	Innopran ;XL tablets	DIFFU CAS multiparticulate bead system comprised of multiple layers of drug, excipients and release controlling polymers	Release is pH independent[20].
27.	Pulsincap	PULSINCAP rupturable system	Release is pH independent[20].
28.	Procardia XL	PROCARDIA XL sutained release tablet	Decrease the frequency of chest pain attacks[20].
29.	Cardizem LA;	CEFORM extended release tablet	Production of uniformly sized and shaped microsphere[20].
30.	ramipril	Polymeric nanoparticles/chitosan	Used to treat high B.P and congestive heart failure (CHF)[20].
31.	Nisoldipine	Solid lipid nanoparticles	Lower high blood pressure[21].
32.	Eplerenone (ARB)	Oral route	Treat high blood pressure[21].
33.	Taladafil (phosphodiesterase-5-inhibitor)	Oral route	Effective in pulmonary hypertension[21].
34.	Imidapril (ACE) inhibitors	By mouth	Manage high blood pressure[21].
35.	Azilsartan (angiotensin-1 receptor blocker)	Orally/40mg or 80mg	Treat hypertension[21].
36.	Macitentan (endothelin A receptor blocker)	Orally/10mg	Pulmonary hypertension[21].
37.	Ambrisentan EARB(endothelinA receptor blocker)	Film coated tablet/orally	Pulmonary HTN[21].
38.	Monoxidine(imidazolidine receptor blocker)	Oral route	Treat mild to moderate essential hypertension[21].
39.	Cicletanine (endothelila nitric oxide synthase coupler)	Orally	It's a diuretic drug for the treatment of hypertension[21].

11. NOVEL BRANDED DRUGS FOR THE TREATMENT OF HYPERTENSION

S. No	Drug	Delivery system/formulation approaches	Applications
1	Flolan (prostacyclin derivative)	Intravenous(I.V)	Treatment of pulmonary arterial hypertension (PAH)[22].
2	Veletri (prostacyclin derivative)	I.V	Treatment of PAH[22].
3	Ventavis (prostacyclin derivative)	Inhaled	Treatment of PAH[22].
4	Remodulin (prostacyclin derivative)	Subcutaneous (SC)/IV	Treatment of PAH[22].
5	Tyvaso (prostacyclin derivative)	Inhaled	Treatment of PAH[22].
6	Tracleer (endothelin receptor antagonist/ERA)	Oral	Treatment of PAH[22].
7	Letairis (ERA)	Oral	Treatment of PAH[22].
8	Revatio (PDE-5-inhibitor)	Oral	Treatment of PAH[22].
9	Adcirca (PDE-5-inhibitor)	Oral	Treatment of PAH[22].

12. NEW COMBINATION THERAPY

S. No	Drug	Delivery system/ formulation approaches	Applications
1	Sildenafil + Epoprostenol	Oral /IV	Treatment of PAH[22].
2	Iloprost + Bosentan	Inhaled /oral	For the treatment of idiopathic pulmonary arterial hypertension (IPAH)[22].

13. HERBAL DRUGS AS BOOM FOR THE MANAGEMENT OF HYPERTENSION:

- The use of herbal medicines throughout the world exceeds as compare to conventional drugs by two to three times.
- It is the oldest form of health care for the prevention and treatment of illness.
- Herbal drugs are phytochemical compounds used for the treatment of many diseases such as hypertension because herb has active ingredients which act as drug.
- Herbal drugs are less expensive than synthetic drugs and people in the rural area mostly used these drugs due to less side effects [23].
- Herbal drugs also have different pharmacokinetic and pharmacodynamic properties which leads to therapeutic responses.

13.1 Advantages of Herbal Medicines:

I. Easily available.
II. Safe and effective.
III. Environmental friendly.
IV. Patient compliant.
V. Fewer side effects as compared to allopathic medicines. [24].

13.2. Herbal drugs which are used as antihypertensive agents:

S.No.	Drug (common name)	Botanical Name	Pharmacological class
1.	Lotus	Nelumbo nucifera	Vasodilator[25].
2.	Ginseng	Panex ginseng	Vasodilator [25].
3.	Garlic	Allium sativum	ACE inhibitors[25].
4.	Snake root	Rouwolfia serpentina	Vasodilator[25].
5.	Ginger	Gingiber officinalis	Vasodilator[25].
6.	Ginko	Ginko biloba	Vasodilator[25].
7.	Hawthorn	Crataegus oxycantha	Vasodilator[25].
8.	Punarnava	Boerhavia diffusa	Diuretic[25].
9.	Ashwagandha	Withania somnifera	Diuretic[25].
10.	Arjuna	Termenalia arjuna	Diuretic[25].
11.	Black cumin seeds	Nigella sativa	Centrally acting[25].
12.	Alpinia	Alpinia zerumbet	Diuretic [25].
13.	Raisins	Vitis vinifera	Vasodilator[25].
14.	Olive leaf	Olea europea	Vasodilator[25].
15.	Beetroot	Beta vulgaris	Nitrodilator[25].
16.	Tea	Camellia sinensis	Nitrodilator/diuretic[26].
17.	Saffron	Crocus sativus	Calcium channel blocker[26].
18.	Roselle	Hibiscus sabdariffa	Calcium channel blocker/vasodilator[26].
19.	King of bitter	Andrographis paniculata	Nitrodilar /ACE-inhibitor[26].
20.	Celery	Apium graveolens	Calcium channel blocker[26].

14. CONCLUSION

The use of combination therapy as first line treatment will help more patients. This review is associated with treatment, management, adverse effects of drugs and diagnosis mainly. There is need for safe and effective therapies to achieve recommended blood pressure targets. This review article also provides help in the detection of B.P. and in the selection of particular antihypertensive drug with herbal drugs.

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