FIXED DOSE COMBINATIONS IN THE TREATMENT OF HYPERTENSION: AN OVERVIEW

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Summary

Hypertension is the major risk factor for Coronary Heart Disease and Stroke. It is difficult to achieve the target blood pressure with one drug. Hence, majority of patients require more than one drug to achieve optimal Blood pressure. Use of antihypertensive fixed dose combinations is recommended by various heart associations. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure report has a recommendation of antihypertensive fixed dose combinations. The use of appropriate combination would maximize the drug action while minimizing the side effects. Patient compliance and low cost of therapy on a long term use have contributed to the increasing use of fixed dose combinations in the treatment of hypertension. There is considerable knowledge about treating patients with hypertension and also appropriate systems to transfer this knowledge world over. It is important on the part of every health care professional to use effectively this knowledge on hypertension for effective treatment of patients.

Keywords: Hypertension, Fixed Dose Combinations, Prevalence, Treatment Guidelines.

Hypertension is designated as silent killer because it causes damage to the body with no symptoms or only mild symptoms and is under-diagnosed. About half of the people diagnosed with abnormal blood pressure have borderline to mildly high blood pressure.

PREVALENCE OF HYPERTENSION

Global prevalence of hypertension

Hypertension is one of the major risk factors for coronary heart disease and stroke [1, 2]. The World Health Organization (WHO) estimated that about 62% of cerebrovascular disease and 49% of ischemic heart disease burden worldwide were due to suboptimal levels of blood pressure. High blood pressure (HBP) is estimated to cause 7.1 million deaths annually, accounting for 13% of all deaths globally [3]. In 2005, around 73 million people (around 39 million females and 34 million males) had HBP and the estimated direct and indirect costs of HBP for 2008 were US$ 69.4 billion.

Prevalence of Hypertension in India

Dubey in 1954 carried out one of the earliest study in India, who documented 4% prevalence of hypertension (criteria:>160/95) amongst industrial workers of Kanpur [4]. In 1984, Wasir et al reported 3% prevalence of hypertension (criteria:>=160/95) in Delhi [5]. During 1984-87 Gopinath et al reported the prevalence of hypertension in Delhi (criteria: >=160/90) to be 11% among males and 12% among females in the urban areas and 4% and 3% respectively in rural areas [6]. Another two studies carried out in rural areas of Haryana (1994-95) demonstrated 4.5% prevalence of hypertension (JNC V criteria) while urban areas of Delhi had a higher prevalence of 45% during 1996-97. Misra et al also reported 12% prevalence of hypertension in the slums of Delhi [7].

In the Indian Council of Medical Research (ICMR) study in 1994 involving 5537 individuals (3050 urban residents and 2487 rural residents) demonstrated 25% and 29% prevalence of hypertension (Criteria:>=140/90 mm of Hg) among males and females respectively in urban Delhi and 13% and 10% in rural Haryana.

Further, Gupta et al, through three serial epidemiological studies (Criteria:>=140/90 mm of Hg) carried out during 1994, 2001 and 2003 demonstrated rising prevalence of hypertension (30%, 36%, and 51% respectively among males and 34%, 38% and 51% among females) [8].

From south India, Kutty carried out hypertension prevalence study (criteria: >=160/95 mm of Hg) in rural Kerala during 1991 in the 20 plus age group and the prevalence was found to be 18%. Later studies in Kerala (Criteria: JNC VI) reported 37% prevalence of hypertension among 30-64 age group in 1998 and 55% among 40-60 age group during 2000. A higher prevalence of 69% and 55% was recorded among elderly populations aged sixty and above in the urban and rural areas respectively during 2000.

Few studies on prevalence on hypertension are available from eastern Indian population. In 2002, Hazarika et al reported 61% prevalence (criteria: JNC VI) among men and women aged thirty and above in Assam [9].

The Sentinel surveillance project, documented 28% overall prevalence of hypertension (criteria: JNC VI) from 10 regions of the country in the age group 20-69. Another study carried out in 1998 among Industrial population in the Bharat Electronics Limited (BEL), India using the same criteria illustrated a prevalence of 30% among men.

Few studies were carried out comparing different socio economic groups. The initial study from urban Chennai, Mohan et al reported 8.4% prevalence of hypertension among men and women aged 20 years and above and belonging to the low socio economic group (based on household income, occupation and dietary pattern) [10]. Similarly, in the middle socio economic group had a higher prevalence (15%) during 1996-97. A study conducted in the urban areas of Chennai during 2000 (age group>=40) reported a higher prevalence of hypertension (54%) among low income group (monthly income < Rs 30000/annum and 40% prevalence among high-income group (monthly income > Rs 60000/annum).

TREATMENT

Treatment challenges

Patient adherence to the therapy is a major challenge while treating patients with hypertension. Patient adherence refers to the willingness and ability of an individual patient to follow health related advice, take medication as prescribed, attend scheduled clinic appointments, and complete recommended tests and consultations [11].

Multiple drugs and complexity of treatment regimen are two most important determinants of poor medication adherence. A survey conducted by the National Council on Patient Information and Education showed that one-third of patients receive at least 2 prescriptions and 10% of patients receive 4 or more prescriptions after a visit to a primary care physician [12]. The study also estimated that the adherence rate is in the range of 30% for chronic conditions.

There is a clear inverse relationship between complexity of the dosing regimen/number of drugs that patients have to take and patient adherence. Adherence to antihypertensive agents varies inversely with dosing frequency [13].

Treatment starts with lifestyle modification, and if BP goal is not achieved, thiazide type diuretics are used as initial therapy for most patients, either alone or in combination with one of the other classes (Angiotensin Converting Enzyme Inhibitors (ACEIs), Angitensin Receptor Blockers (ARBs), Beta Blockers (BBs), Calcium Channel Blockers (CCBs)) (Tables 1 and 2). Selection of one of these agents alone as initial therapy is recommended when a diuretic cannot be used or when a compelling indication is present that requires the use of a specific drug. If the initial drug selected is not tolerated or is contraindicated, then a drug from one of the other classes proven to reduce cardiovascular events should be substituted. Since most hypertensive patients will require two or more antihypertensive medications to achieve their BP goals, addition of a second drug from a different class should be initiated when use of a single agent in adequate doses fails to achieve the goal. When BP is >20 mmHg above systolic goal or 10 mmHg above diastolic goal, consideration is given to initiate therapy with two drugs, either as separate prescriptions or in fixed-dose combinations (Figure 1) [14].

Following options are usually followed by majority of physicians:
Option 1: Lifestyle modification
Option 2: Patient put on monotherapy and slight increase in the dose of the drug until target blood level is achieved
Option 3: Trial of sequential monotherapy until an effective agent is found.
Options 4: Use of more than one drug either individual or a fixed dose combinations

Figure 1 – Algorithm for Treatment of Hypertension

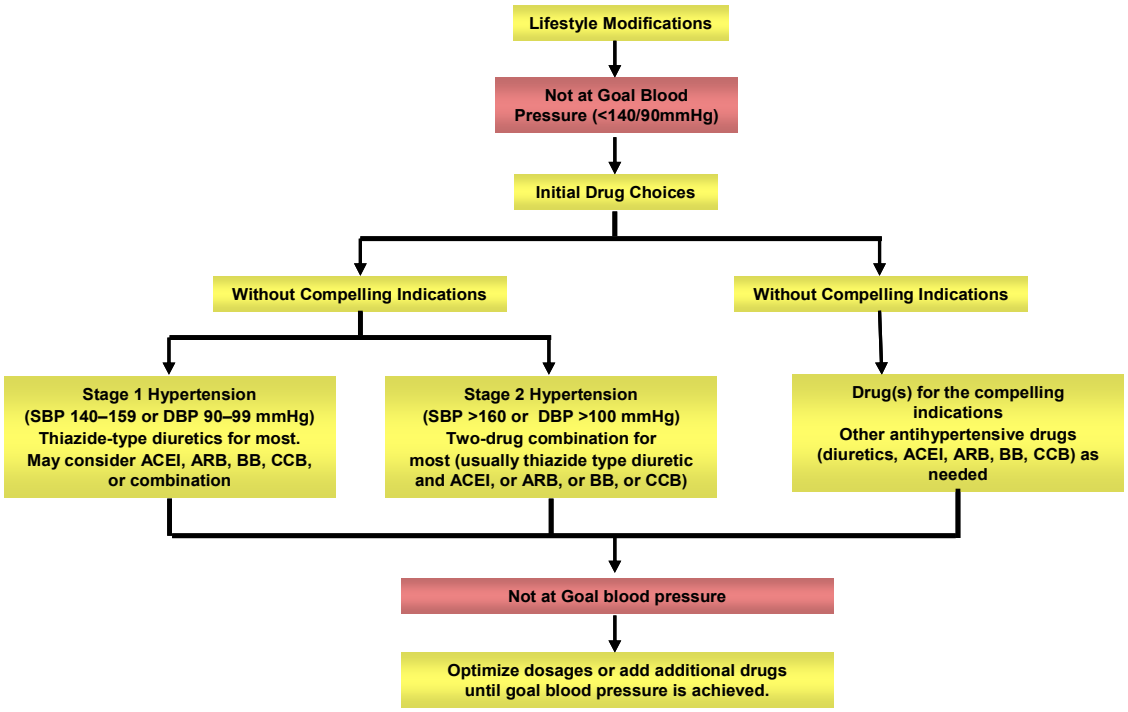

Table 1 – Antihypertensive Drug Classification

Class	Example
Diuretics A) Thiazide diuretics	Chlorothiazide, Chlorthalidone, Hydrochlorothiazide, Polythiazide, Indapamide, Metolazone
B) Loop diuretics	Bumetanide, Furosemide, Torsemide
C)Potassium sparing diuretics	Amiloride, Triamterene
Aldosterone receptor blockers	Eplerenone, Spironolactone
Beta blockers	Atenolol, Betaxolol, Bisoprolol, Metoprolol, Nadolol, Propranolol, Timolol
Beta blockers with intrinsic sympathomimetic activity combined alpha and beta blockers	Acebutolol, Penbutolol, Pindolol, Carvedilol, Labetalol
Angiotensin converting enzyme inhibitors	Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Perindopril, Quinapril, Ramipril, Trandolapril
Angiotensin antagonists	Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan
Calcium channel blockers A) Dihydropyridines	Amlodipine, Felodipine, Isradipine, Nicardipine, Nifedipine, Nisoldipine
B) Non Dihydropyridines	Diltiazem, Verapamil
Alpha-1 blockers	Doxazosin, Prazosin, Terazosin
Central Alpha-2 agonists and other centrally acting drugs	Clonidine, Methyldopa, Reserpine, Guanfacine
Direct vasodilators	Hydralazine, Minoxidil

Table 2 – Antihypertensive Combination Drugs

Combination	Example
ACEIs and CCBs	Amlodipine+Benazepril hydrochloride
	Enalapril+Felodipine
	Trandolapril+Verapamil
ACEIs and diuretics	Benazepril+Hydrochlorothiazide
	Captopril+Hydrochlorothiazide
	Enalapril+Hydrochlorothiazide
	Fosinopril+Hydrochlorothiazide
ARBs and diuretics	Candesartan+Hydrochlorothiazide
	Eprosartan+Hydrochlorothiazide
	Irbesartan+Hydrochlorothiazide
	Valsartan+Hydrochlorothiazide
BBs and diuretics	Atenolol+Chlorthalidone
	Bisoprolol+Hydrochlorothiazide
	Metoprolol+Hydrochlorothiazide
	Nadolol+Bendroflumetazide
	Timolol+Hydrochlorothiazide
	Propranolol LA+Hydrochlorothiazide
Centrally acting drug and diuretic	Methyldopa+Hydrochlorothiazide
	Reserpine+Chlorthalidone
	Reserpine+Chlorothiazide
	Reserpine+Hydrochlorothiazide
Diuretic and diuretic	Amiloride+Hydrochlorothiazide
	Spironolactone+Hydrochlorothiazide
	Triamterene+Hydrochlorothiazide

ACEIs – Angiotensin converting enzyme inhibitors, ARBs – Angiotensin Receptor Blockers, BBs – Beta Blockers, CCBs – Calcium Channel Blockers

The initial step in treating mild hypertension is by non-pharmacological treatment like diet (includes reduced sodium intake), lifestyle changes, regular exercise, stress management and self-monitoring with a home blood pressure device. Weight reduction even without sodium restriction has been shown to normalize blood pressure in up to 75% of overweight with mild to moderate hypertension.

Mild hypertension is also treated by pharmacological means with single drug therapy. Thiazide diuretics, ß-blockers and ACE inhibitors have been shown to reduce morbidity and mortality and are recommended for initial drug therapy. If a single drug therapy does not adequately control blood pressure, drugs with different sites of action are combined to effectively lower blood pressure while minimizing toxicity.

The main goal of antihypertensive therapy is to prevent, arrest or reverse target organ damage (TOD) in patients with hypertension. There are a few guidelines which help physicians to attain adequate level of blood pressure levels. JNC (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) is the most preferred document which is followed by most of the physicians all over the world.

Recent, the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) was published in 2003 and has major implications for the physicians through out the world [15].

Table 3 – Change in Blood Pressure Classification

JNC 6 category		JNC 7 category
	SBC/DBP	
Optimal	<120/80	**Normal**
Normal	120-129/80-84	**Pre hypertension**
Borderline	130-139/85-89	
Hypertension	≥140/90	**Hypertension**
Stage 1	140-149/90-99	**Stage 1**
Stage 2	160-179/100-109	**Stage 2**
Stage 3	≥180/110	

A few important aspects which were stressed in JNC 7 report are as follows:
1. Incremental risk of cardiovascular disease (CVD) begins at much lower levels (115/75mmHg) of systolic blood pressure (SBP).
2. Persons with blood pressure (BP) level of SBP 120-139 or diastolic blood pressure (DBP) levels of 80-89 mmHg were labeled as "prehypertensive" than "High Normal" (Table 3).
3. Stage 1 hypertension of JNC-6 is retained, stage 2 and 3 are named stage 2 for ease of management.
4. Persons older than 50 years, SBP > 140 mmHg is a much more important risk factor for cardiovascular disease than DBP,
5. A much greater importance has been given to the use of thiazide-type diuretics as the preferred first line therapy than it was being done in the past.
6. The importance of using more than one class of drugs earlier than was the case hitherto has been highlighted. The new recommendations says that whenever BP is more than 20/10 mmHg above the goal BP, use of 2 classes of drugs should be considered and one of these should be a thiazide-type diuretic.
7. The importance of interaction with and motivation of the patient on prevention of hypertension and reducing its cardiovascular events has been stressed.

Finally, JNC 7 also highlights the fact that in spite of increasing knowledge about hypertension, the healthcare systems all over the world have failed to translate knowledge about hypertension into action.

The rates of achieving goal blood pressure are currently inadequately low throughout the world. In India, the rates are even lower because of cost of investigations, cost of medication, lack of follow-up. Moreover, there is no practice of monitoring blood pressure at home. This may also considerably contribute to low rates of achieving optimal blood pressure. Poor adherence to therapy is a major reason that large percentage of patients with hypertension fail to achieve good blood pressure control [16].

Another much neglected reason for achieving low rates of goal blood pressure is persistence with a single class of drug for too long, while the patient is lost to follow-up. Failure to achieve goal blood pressure is particularly common in the case of SBP.

Importance of two or more Antihypertensives to Achieve Goal Blood Pressure
First ever fixed dose combinations (reserpine+hydralazine+hydrochlorthiazide and methyldopa+hydrochlorthiazide) for the treatment hypertension became available in 1961 [14].

The Veteran's Administration Cooperative Study on Antihypertensive Agents was the very earliest outcome trial of antihypertensive therapy, demonstrated dramatic reductions in CV outcomes with a triple combination of hydrochlorthiazide, reserpine, and hydralazine compared with placebo [17].

Most patients with hypertension need two or more antihypertensive medications to achieve goal blood pressure. ALLHAT (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) [18] have clearly shown that more than two thirds of the patients require two or more drugs to bring their BP to target level. Many current guidelines have recommended the use of combination therapy as first-line treatment, or early in the management of hypertension in patients with comorbidities that require prompt BP reduction. Initial treatment with 2 antihypertensive agents is suggested for persons with BP >20/10 mmHg above goal [19, 20]. Use of fixed dose combinations where low-dose combination of individual drugs are effective than the respective high dose monotherapies (Example: amlodipine besylate/benazapril HCl and telmisartan/hydrochlorothiazide) in first-line therapy are recommended [21]. The problem perhaps lies with the multifactorial nature of hypertension as suppression of one factor is counteracted by another physiological mechanism and patient adherence.

As hypertension is multifactorial and many pathophysiologic factors contribute to high BP, the combination of agents with different (and complementary) mechanisms of action provides more complete blockade of pressor mechanisms with less activation of counter regulatory mechanisms. For example, diuretics activate the renin-angiotensin-aldosterone system (RAAS), reduce volume, and make BP more angiotensin dependent. Concomitant administration of an ACE inhibitor or an angiotensin II receptor blocker (ARB) blocks angiotensin II generation or action, minimizing the compensatory pressor effect of diuretic-induced RAAS activation and producing an additive BP-lowering effect.

Adherence to antihypertensive treatment increases with fixed-dose combinations. Adherence to a fixed-dose combination of the calcium channel blocker (CCB) amlodipine with the angiotensin converting-enzyme (ACE) inhibitor benazepril has been compared with adherence to free-dose combination therapy of the two agents in a retrospective analysis of data obtained from a pharmacy claims database in the US [22].

It is also clearly recommended by JNC-7 that addition of a second drug from a different class should be initiated when a single drug in adequate doses fails to achieve goal blood pressure. JNC-7 has also endorsed the use of combination therapy in stage 2 patients as a direct approach. The new guidelines recommend that if blood pressure is more than 20/10 mmHg above goal blood pressure (<140/90 mmHg or <130/80 mmHg in diabetic and in CKD patients) then one should consider even initiating therapy with two drugs, one of which should be a thiazide type diuretic. In order to take care of cost, confusion and compliance the use of fixed dose combinations should be considered.

Fixed dose combinations offer the advantage of ease of administration ensuring better compliance, reduced dose of each component resulting in fewer side effects and additive or synergistic effects of the components resulting in better control of hypertension without the interference of compensatory mechanisms.

In India most patients will not visit the hospital or physician for optimization of monotherapy or complain of too many drugs or doses. A fixed dose combination to control hypertension seems to be a better option.

CONCLUSION

Hypertension awareness has not changed in the last 10 years, treatment rates have increased only slightly, while the control rates remain stagnant at around 30%. Failure on the part of healthcare system continues to add every year to the burden of hypertensive morbidity and mortality.

JNC 7 report and other guidelines authorized use of two or more drug combinations which would lower over cost of therapy, increase adherence and compliance.

There is considerable knowledge about treating patients with hypertension and also appropriate systems to transfer this knowledge world over. It is important on the part of every health care professional to use effectively this knowledge on hypertension for effective treatment of patients.

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