



Original Research Article

Patterns of antihypertensive drug distribution of patients with hypertensive diabetes mellitus: A Hospital based observational study

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Abstract

Objectives: *This present study was to evaluate the pattern of antihypertensive drug distribution as monotherapy, combination therapy and fixed dose combination of patients with hypertensive diabetes mellitus.*

Methodology: *A total of 100 patients of hypertensive diabetes mellitus were enrolled in this study. A detail history, complete assessment and relevant investigation were taken to all patients. Pattern of drug prescription was monotherapy, combination therapy and fixed dose combination.*

Results: *Data was analyzed by using simple statistical methods with the help of MS-Office software.*

Conclusions: *Patients of hypertensive diabetes mellitus was commonly seen in beyond 4th decades of life. Calcium channel blockers (amlodipine) and ACE inhibitors (Enalapril, ramipiril, lisinopril, levipril) were greatly prescribed in patients of hypertensive diabetes mellitus as monotherapy. AT II blocker with diuretics, ACE inhibitors with diuretics and β blocker with Calcium channel blocker were commonly used as combination therapy. And as a fixed dose combination therapy calcium channel blockers with angiotensine II receptor blocker and β blockers with diuretics were prescribed in majorities of patients with hypertensive diabetes mellitus. In mild to moderate HTN, the first line of treatment was lifestyle modification, i.e., weight control, low fat anti-atherogenic diet, salt restriction, reduction in alcohol intake, discontinuation of smoking, and some regimens of physical activity.*

Keywords: *Hypertension, Hypertensive diabetes mellitus, Antihypertensive drug prescription.*

Introduction

Management of hypertension in diabetics demands special attention, more so in Indian scenario. Higher prevalence of hypertension (HTN) amongst diabetics in India has been reported since 1985.^[1] Review on the subject by Das in 1995 (on Indian data) had revealed the prevalence to be as variable as 7 per cent in

Cuttack to 30.9 per cent at Sevagram^[2]. Further, there was a variable difference between IDDM (Type-1) and NIDDM (Type-2) i.e., 10 versus 32 per cent respectively in diabetics from Mumbai. Studies from Manipal revealed about 40 per cent diabetics to be hypertensive^[3]. Such higher prevalence of HTN could partly be due to better assessment in diabetics but most likely on par

with change of lifestyle and increase in the prevalence of noncommunicable diseases in rapidly growing economies.^[4]

India currently has 40.9 million diabetic patients and it is expected to rise to is expected to rise to 69.9 million by 2025 unless urgent and effective preventive steps are taken.^[5] One and half billion people will suffer from hypertension and 300 million will suffer from diabetes by 2025.^[6,7] Prevalence of hypertension is 60% in type 2 DM.^[8] Patients with T2DM has two fold higher chances of suffering from hypertension in comparison to age match subjects without diabetes.^[9] Hypertension has been shown as a major risk factor not only for the development of diabetes but also for the development of micro and macro vascular complications like neuropathy, nephropathy, retinopathy, coronary artery disease, stroke, Peripheral Vascular Disease (PVD) in diabetic patients.^[10]

Aim of our study was to evaluate the prescribing pattern of antihypertensive drugs for the management of hypertensive diabetes mellitus patients to achieve minimum complication.

Materials & Methods

This present study was conducted in department of Pharmacology with the collaboration of department of Medicine, Katihar Medical College and Hospital, Katihar, Bihar, India during a period from February 2017 to October 2017.

A total of 100 patients of hypertension with diabetes mellitus of age group less than 30 years to greater than 75 years were enrolled in this study. Entire subjects signed an informed consent approved by institutional ethical committee of Katihar Medical College, Katihar, Bihar India was sought.

Methods

Data was collected by using random sampling methods. Inclusion criteria of this study was the patients of hypertension with diabetes mellitus taking treatment from department of Medicine, Katihar Medical College and Hospital, Katihar,

Bihar. Patients of diabetes mellitus with hypertension who were suffering from any other diseases like lungs diseases, cardiac diseases, metases, e.t.c were excluded from this study. Monotherapy, combination therapy and fixed dose combination were used as patterns of drug prescription in patients of hypertension with diabetes mellitus.

Statistical Analysis

Data was analyzed by using simple statistical methods with the help of MS-Office software.

Observations

This study was conducted in department of Pharmacology, Katihar Medical College, Katihar, Bihar, India.

In this present study, we were enrolled the patients with age less than 30 years to age greater than 75 years. Out of total 100 patients, 60 patients were males and 40 patients were females. Male and female ratio was 3:2.

Table. 1 Age wise distribution of patients with hypertensive diabetes mellitus.

Age(Years)	No. of patients	Percentage
< 30 years	3	3%
31-45	10	10%
46-60	45	45%
61-75	30	30%
>75	12	12%
Total	100	100%

Majorities of cases 45(45%) of diabetes with hypertension were in age group of 46 years to 60 years.

Table.2. Categories wise drug distribution in hypertensive diabetes mellitus patients.

Categories of drugs	No. of cases	Percentage
Calcium channel blockers amlodipine	24	24%
ACE inhibitors (Enalapril, ramipiril, lisinopril, levipril)	20	20%
Diuretics (furesamide, torsemide)	16	16%
β blockers (atenolol)	10	10%
K ⁺ opener (nicorandril)	3	3%

In this study, we were found that calcium channel blockers amlodipine was prescribed in majorities of diabetes mellitus with hypertension patients

24(24%) as a monotherapy. ACE inhibitor was prescribed in 20 (20%) diabetes with hypertension patients.

Table.3 Combination of drugs distribution

Category of drugs	No. of cases	Percentage
AT II blocker + diuretics	26	26%
ACE inhibitors + diuretics	10	10%
β blocker + Calcium channel blocker	10	10%
Calcium channel blocker + ACE inhibitor	7	7%
AT II blocker + ACE inhibitors	7	7%
Calcium channel blocker + diuretics	7	7%
B blocker + AT II blocker	7	7%

In this present study, combination of antihypertensive drugs was also used in the cases of diabetic mellitus.

AT II blockers with diuretics was prescribed by the Physicians in maximum number of cases 26(26%). ACE inhibitors with diuretics and B blocker with calcium channel blocker were prescribed in 10(10%) patients of diabetes mellitus. Calcium channel blocker with ACE inhibitor, AT II blocker with ACE inhibitor and calcium channel blocker with diuretics were prescribed in 7(7%) patients of diabetes mellitus.

Table 4. Fixed dose combination of drug distribution in hypertensive diabetes mellitus patients

Categories of drugs	No. of cases	Percentage
β blockers + diuretics	28	28%
Calcium channel blockers + angiotensine II receptor blocker	46	46%
ACE inhibitors + diuretics	19	19%
AT II blocker + diuretics	10	10%

In this present study, calcium channel blockers with angiotensine II receptor blocker were prescribed in majorities of patients 46(46%) of diabetes with hypertension as a fixed dose combination.

Table. 5 Aspirine distribution in hypertensive diabetes mellitus patients.

Drugs	No. of cases	Percentage
Aspirine used	5	5%
Aspirine not prescribed	95	95%

Aspirine was prescribed by Physician in only 5(5%) patients of hypertension with diabetes mellitus.

Table.6 Lipid lowering drugs (LLD) distributions in hypertensive diabetes mellitus patients.

Drugs	No. of cases	Percentage
LLD prescribed	14	14%
LLD not prescribed	86	86%

In this present study, lipid lowering drugs was prescribed by the Physicians in 14(14%) of patients of hypertension with diabetes mellitus

Discussion

Hypertension and Diabetes are life style disease and are the major burden of global Health due to complications.

Hypertension has a major risk factor not only for the development of diabetes but also for the development of micro and macro vascular complications like neuropathy, nephropathy, retinopathy, coronary artery disease, stroke, Peripheral Vascular Disease (PVD) in diabetic patients. The benefits of Blood Pressure (BP) control in diabetic patients exceed the benefits of tight glycemic control and vital to the prevent and retard progression of both microvascular and macrovascular complications of hyperglycemias.^[11] Therefore, all of the hypertension management guidelines, that is, eighth report of Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure-2013 (JNC-8),^[12] American Diabetes association (ADA) 2014^[13] and European Society of Hypertension (ESH 2013)^[14] focused aggressively on Blood Pressure (BP) control in diabetic patient to below 140/80-90 mmHg. JNC 8 recommended target of diastolic BP <90 mmHg and ESC 2013 recommended <85 mmHg. But ADA recommended target of DBP <80 mmHg. There are limited data from India regarding physician's choices of anti-hypertensive therapies for a patient with diabetes in single- and multiple-drug based regimens.^[10]

Khrime D, et al. (2015)^[10] were conducted a study of utilisation of antihypertensive drugs for the patients of hypertensive diabetes mellitus. They

were enrolled 223 patients with age group of 18-86 years and in their study male and female ratio was 1.18: 1.

In our present study, we were enrolled a total of 100 patients with age group less than 18 years to greater than 30 years. Male and female ratio was 3:2. Majorities of cases 45(45%) of hypertensive diabetes mellitus were belonged in age group of 46 years to 60 years.

In diabetic patients, particularly those with mild to moderate HTN, the first line of treatment includes lifestyle modification, i.e., weight control, low fat anti-atherogenic diet, salt restriction, reduction in alcohol intake, discontinuation of smoking, and supervised regimens of physical activity. The next step would be administration of antihypertensive drugs. Five classes of drugs are considered to be effective for monotherapy. Diuretics, beta-blockers, calcium channel blocker, alpha 1 adrenergic blockers, ACE-inhibitors, and likely angiotensin-receptor antagonists are the armamentarium of first line drugs available for use in India. In the absence of randomised controlled large scale clinical trials on the various classes of antihypertensive agents in diabetic patients with HTN, the choice of treatment is based on our understanding of the pathophysiology of HTN in diabetics and known pharmacological action as well as side-effects of the drug to be administered.^[4]

Our study was supported the findings of Khrame D, et al. (2015).^[10] In their study monotherapy was needed in 46.18% (n =103) patients and dual therapy was required in 32.73% (n=73) patients. Thirty nine patients (17.48%) were on triple drug therapy and eight patients (8.07%) were on quadruple drug therapy.

Use of multiple drugs in combinations is being increasingly recognized as critical to control hypertension in patients with diabetes. Fixed-dose combination (FDC) therapies offer a means to simplify complex treatment regimens, and have several advantages that help patients reach their glycaemic goals. Recently, several large clinical trials demonstrated that most patients with

hypertension can achieve and sustain adequate blood pressure control only with the use of multiple antihypertensive drugs. Initiating drug therapy with a diuretic, either alone or in combination with an agent from another drug class apparently provides the best outcomes for hypertension management as per the JNC VII and JNC VIII guidelines.

In our study, calcium channel blockers amlodipine was prescribed in majorities of hypertensive diabetes mellitus patients 24(24%) as a monotherapy. ACE inhibitor was prescribed in 20 (20%) patients. AT II blockers with diuretics was prescribed by the Physicians in maximum number of cases 26(26%). ACE inhibitors with diuretics and B blocker with calcium channel blocker were prescribed in 10(10%) patients of diabetes mellitus. Calcium channel blocker with ACE inhibitor, AT II blocker with ACE inhibitor and calcium channel blocker with diuretics were prescribed in 7(7%) patients of diabetes mellitus. Calcium channel blockers with angiotensin II receptor blocker were prescribed in majorities of patients 46(46%) of diabetes with hypertension as a fixed dose combination.

The SHEP study^[15] using low dose diuretics, beta blockers, calcium channel blockers, ACE-inhibitors and the SYST – EUR study^[16] using calcium channel blockers and ACE – inhibitors with diuretics as reserve, have shown beneficial effects of BP control as concluded by extension of UKPD study group alluded to above. It is to be noted that both SHEP and SYST-EUR Study recruited diabetic hypertensives also for the trials. The International Diabetic Federation Consensus guidelines^[17] have anticipated reduction in stroke morbidity and mortality, heart failure morbidity and mortality, in CAD events and reduction in progression of renal disease including diabetic nephropathy by tight control of hypertension in DM. Reduced left ventricular hypertrophy, a marker for CAD and HF was anticipated as a relevant surrogate outcome. The above list does not include the benefit of management of malignant HTN.

In the UKPDS epidemiological study, each 10 mm Hg decrease in the mean systolic BP was associated with reduction in risk of 12% for any complication related to DM, 15% for deaths related to DM, 11% for myocardial infarction, and 13% for microvascular complications.^[35]

The UK PDS suggests that blood pressure reduction itself may be more important than the measures used to achieve it, but ACE inhibitors were better tolerated. Systolic hypertension in the elderly (SHEP) trial, Hypertension Optimal Study (HOTstudy)^[18] and SYST-EUR study used β -Blockers and/or diuretics and many of the subjects included in the trials were diabetic. All these trials demonstrated beneficial effects of treatment in reducing cardiovascular mortality and morbidity^[19]. Low dose thiazides, beta-blockers, ACE inhibitors, dihydropyridine calcium channel blockers (long acting) have all shown benefits in type-2 DM^[20]. That both older (beta blockers, diuretics) and newer drugs (ACE inhibitors, calcium channel blockers, alpha-blockers, and angiotension-II receptor, blockers) have equal efficacy have been proved by various trials. They all reduce mortality and morbidity of CV events in hypertensives (even those with DM) and they all improve the quality of life^[21,22].

ACE inhibitors have renoprotective effect by reducing intraglomerular pressure. They reduce albuminuria in diabetic nephropathy, reduce rate of renal deterioration, and have no adverse effect on lipids. They minimise adverse metabolic effects of diuretics^[23,24] and may have a specific role if nephropathy is present in type-1DM^[20]. They may potentiate the hypoglycaemic effect of insulin and oral antidiabetic drugs^[20]. Irritable cough and very rarely angio-oedema, are the important side effects. Hypoglycaemia, hyperkalaemia, and rise of serum creatinine should be watched. These drugs are contraindicated in bilateral renal artery stenosis, pregnancy, and lactation. Angiotensin-II receptor blockers have many properties similar to those of ACE-inhibitors. As they don't inhibit the breakdown of bradykinin and other kinins, cough

is not a problem with their use¹. These drugs (losartan potassium, candesartan, valsartan, etc.) should be used with caution in unilateral renal artery stenosis, aortic or mitral valve stenosis and in hypertrophic obstructive cardiomyopathy^[26].

Calcium channel blockers^[27]: Only long acting dihydropyridines (nifedipine-retard, amlodipin, lacidipin) are used. Amlodipin does not have negative inotropic effects and can be used in diabetic hypertensives with heart failure. Ca-channel blockers are also useful in angina, especially Prinzmetals' angina. Pedal oedema and headache are the side effects: Gingival hyperplasia may occur^[23,20]. When data from all comparative trials of using various drugs in almost 5,000 hypertensive diabetics are combined, the lowest mortality rate has been found with calcium channel blocker based therapy^[28].

Combination of ACE inhibitors and ARB reduce retinal and other ocular complications and lower the level of uric acid seen in diabetic nephropathy. This combination reduces both preload and afterload in patients with subclinical or overt hypertensive heart failure. This combination having a low effective dose of both these agents, the chances of dry cough are reduced much more than monotherapy with ACE-inhibitors or A II^[29]. HOT study, Thrombosis Prevention Trial and ALLAHAT Trial have shown that 75 mg aspirin OD reduces major CV events by 15% but not fatal events, in hypertension especially in diabetes. This is indicated in patients aged 50 years or above, if 10 years CAD– risk is $\geq 15\%$, if serum cholesterol is ≥ 5 mmol/L and if TOD and CCD exist. The incidence of CAD is definitely reduced.^[18,22]

In this present study, Aspirine was prescribed by Physician in only 5(5%) patients of hypertensive diabetes mellitus. And lipid lowering drugs was prescribed in 14(14%) of patients of hypertension with diabetes mellitus.

According to Joint British Recommendation on Prevention of CAD and Scottish Inter-Collegiate Guidelines, statins lower coronary events, stroke and all cause mortality and are safe, simple, and well tolerated. Statins are indicated in diabetic

hypertension upto age 75 years if serum cholesterol is ≥ 5 mmol/L and 10 year CAD risk $\geq 30\%$ especially if patient is having angina or MI. Statins lower blood pressure also and they correct dyslipidaemia that commonly accompanies DM^[28].

Combination therapy may also be more beneficial than monotherapy in reducing the risk of cardiovascular events. In the Fosinopril Versus Amlodopine Cardiovascular Events Randomized Trial,^[30] those who received the combination of amlodipine and fosinopril had fewer cardiovascular events than those who received either drug alone. Bakris et al ^[31,32] documented that at comparable BP levels the combination of an ACE inhibitor (either lisinopril or trandolapril) and verapamil was more effective than either drug alone in attenuating both albuminuria and the rate of decline in glomerular filtration rate. The use of a combination of an ACE inhibitor and calcium antagonist is strongly recommended to maximally protect the kidney in diabetic hypertensive patients with nephropathy.^[33,34]

Conclusions

This present study was concluded that patients of hypertensive diabetes mellitus were commonly seen in age > 45 years. Calcium channel blockers (amlodipine) and ACE inhibitors (Enalapril, ramipiril, lisinopril, levipril) were greatly prescribed in patients of hypertensive diabetes mellitus as monotherapy. AT II blocker with diuretics, ACE inhibitors with diuretics and β blocker with Calcium channel blocker were commonly used as combination therapy. And as a fixed dose combination therapy calcium channel blockers with angiotensine II receptor blocker and β blockers with diuretics were prescribed in majorities of patients with hypertensive diabetes mellitus. In mild to moderate HTN, the first line of treatment was lifestyle modification, i.e., weight control, low fat anti-atherogenic diet, salt restriction, reduction in alcohol intake, discontinuation of smoking, and some regimens of physical activity.

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