

## A STUDY OF ADVERSE EFFECTS PROFILE OF VARIOUS ANTIHYPERTENSIVE DRUGS AMONG HYPERTENSIVE PATIENTS IN A TERTIARY CARE CENTRE

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### ABSTRACT

#### BACKGROUND

Hypertension is the leading cause of morbidity and mortality worldwide. The aim of hypertensive therapy is to prevent morbidity and mortality associated with persistent raised BP by lowering it to an acceptable level. Antihypertensive drugs are frequently associated with undesirable effects that may limit treatment options and reduce patient adherence to treatment. Because hypertension is an asymptomatic disorder and requires long term therapy, consideration of potential adverse effects of drugs used for its treatment is important for making appropriate choice.

Aim of the study was to assess the adverse effect profile of various antihypertensives prescribed at a tertiary care centre.

#### MATERIALS AND METHODS

The study was an observational study conducted by face-to-face interview among mild-to-moderate hypertensive patients who received antihypertensive as a monotherapy or combined drug therapy not less than three months, attending medicine outpatient department on a daily basis for a period of 12 months. Study was approved by the institutional ethics committee; informed consent form was obtained from the patients participating in the study.

#### RESULTS

Total 2080 patients who were on hypertensives, 40.77% patients were on monotherapy and 59.23% patients were on combined drug therapy. Adverse effects were observed among 1003 patients and were more in patients with combination therapy (62.11%) than patients on monotherapy (37.89%). Among monotherapy, Enalapril was associated with most adverse effects (17.15%) as compared to Amlodipine (13.66%) and Atenolol (7.08%). Triple therapy (37.09%) was associated with more adverse effects as compared to dual therapy (25.02%).

#### CONCLUSION

At a tertiary care centre, enalapril and amlodipine were most commonly prescribed drugs while enalapril was most commonly associated with adverse effects as compared to amlodipine and atenolol. The combination therapy was associated with more adverse effects as compared to monotherapy in the present study. This study setting was institutional based which may not be generalised. However, assessment of adverse effects associated with use of antihypertensive drugs should be done continuously to prevent treatment dropout and improve patient's adherence to treatment.

#### KEYWORDS

Adverse Effects, Antihypertensive Drugs, Hypertensive Patients.

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#### BACKGROUND

Hypertension is the leading cause of morbidity and mortality worldwide. The World Health Organization (WHO) report which examined the major risk factors for global disease identified hypertension as one of the most important cause of the disease burden of developed and developing nations.<sup>1</sup>

Blood pressure is expressed by two measurements, the systolic and diastolic pressures which are the maximum and minimum pressures respectively. Normal blood pressure at rest is within the range of 100 to 140 mm of Hg systolic and 60 to 100 mm of Hg diastolic.<sup>2</sup> High blood pressure is present if

the resting blood pressure is persistently at or above 140/90 mm of Hg for most adults.<sup>3</sup> The epidemiological studies of last 20 years show that prevalence of hypertension in urban location has stabilised to about 20-30% but it has increased in rural population from 15 to 25%.<sup>4</sup> Residual lifetime risk for developing hypertension in middle-aged and elderly individuals is 90%, indicating a huge public health burden.<sup>5</sup> The aim of hypertensive therapy is to prevent morbidity and mortality associated with persistent raised BP by lowering it to an acceptable level with minimum inconvenience to the patient. Compared with other known risk factors for acute myocardial infarction, heart failure, stroke, end-stage renal disease, hypertension is perhaps the simplest to diagnose, easiest to treat and one of the most cost effective preventive strategies.<sup>6</sup> For the treatment of hypertension, a broad range of antihypertensive medications are currently available. Evidence suggests that reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischaemic heart disease by 21%, and reduce the likelihood of dementia, heart failure and mortality from cardiovascular disease.<sup>7</sup>

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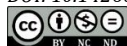
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Antihypertensive drugs are frequently associated with undesirable effects that may limit treatment options and reduce patient adherence, which may hinder blood pressure control. It is thought that different discontinuation rates for various classes of antihypertensives are probably related to their different rates of adverse symptoms. Because hypertension is an asymptomatic disorder and requires long-term therapy,<sup>8</sup> consideration of potential undesirable effects of drugs used for its treatment is important for making appropriate choice. In this context, precise understanding of efficacy and adverse effect profile of different antihypertensive drugs is essential. Monitoring of adverse effects of drug is more important in case of chronic ailments such as hypertension. A good control of blood pressure and avoidance of adverse effect can, however, be achieved by appropriate drug selection and dosage, carried out after careful consideration of known adverse effect profile of different compounds in reducing blood pressure.

Amlodipine, atenolol and enalapril are commonly prescribed antihypertensives in our tertiary care centre. Calcium channel antagonists enjoy a reputation of efficacy and tolerability. They can be used in patients with diabetes mellitus, hyperlipidaemia, coronary artery disease, asthma, gout. Amlodipine is a long-acting dihydropyridine calcium antagonist indicated for both hypertension and angina. Unlike older short-acting dihydropyridines, it is safe in patients with heart disease.<sup>9</sup> The most common side effects caused by this class of drug, particularly the dihydropyridines, are due to excessive vasodilation. Symptoms include dizziness, hypotension, headache, flushing, digital dysaesthesia, and nausea. Patients also may experience constipation, peripheral oedema, coughing, wheezing, and pulmonary oedema.<sup>10</sup> Beta blockers have been widely used in the treatment of hypertension. However, this class of drug is contraindicated in patients with asthma, bradyarrhythmias and peripheral vascular disease. Atenolol is beta-adrenergic blocking agent that has shown to be effective given once daily as monotherapy in treatment of hypertension.<sup>11</sup> Adverse effects associated with the use of beta blockers include: nausea, diarrhoea, bronchospasm, dyspnoea, cold extremities, bradycardia, hypotension, heart failure, heart block, fatigue, dizziness, abnormal vision, decreased concentration, hallucinations, insomnia, nightmares, clinical depression, sexual dysfunction, erectile dysfunction and/or alteration of glucose and lipid metabolism.<sup>10</sup> Enalapril is an angiotensin converting enzyme inhibitor which is used in hypertension as once daily dose of 5 mg titrated upwards up to 40 mg.<sup>12</sup> Side effects common to all ACE inhibitors include acute renal failure, hyperkalaemia, dry cough sometimes accompanied by wheezing, and angioedema. Minor toxic effects seen more typically include altered sense of taste, allergic skin rashes, and drug fever, which may occur in as many as 10% of patients.<sup>10</sup>

The result of adverse effect profile would provide the necessary information on adverse effects of different antihypertensive medications. So the objective of this study was to evaluate the incidence of adverse effects in patients receiving antihypertensive drugs at the tertiary care centre.

## MATERIALS AND METHODS

The study was an observational study, conducted by face-to-face interview among mild-to-moderate hypertensive patients who received antihypertensive medicines not less than three

months, attending medicine outpatient department on a daily basis in a tertiary care centre for a period of 12 months. Study was approved by the institutional ethics committee, informed consent form was obtained from the patients participating in the study. The aim of the study was to assess adverse effect profile of various antihypertensives prescribed at the tertiary care centre as a monotherapy or combined drug therapy. All patients taking other than antihypertensive medication, patients having other comorbid conditions like IHD, heart failure, COPD, diabetic mellitus, peripheral vascular disease, cardiomyopathy & mentally compromised or unconscious patients and patients unable to respond to verbal questions were excluded from the study. They were asked about adverse effects which they felt after taking medication. The data collected through questionnaire was organised, tabulated, results were calculated on basis of Microsoft Excel and analysed by using statistics such as percentage, mean, standard deviation, etc.

## RESULTS

Of total 2080 hypertensive patients, 1224 (58.85%) were males and 856 (41.15%) were females (FIG.1). Out of 2080 patients, 848 (40.77%) patients were on monotherapy and 1232 (59.23%) patients were on combined drug therapy (FIG.2). Adverse effects were observed among 1003 (48.22%) patients, among which females 514 (24.71%) were more as compared to males 489 (23.50%). The most vulnerable age group with maximum adverse effects was 41-60 years. (Table 1)

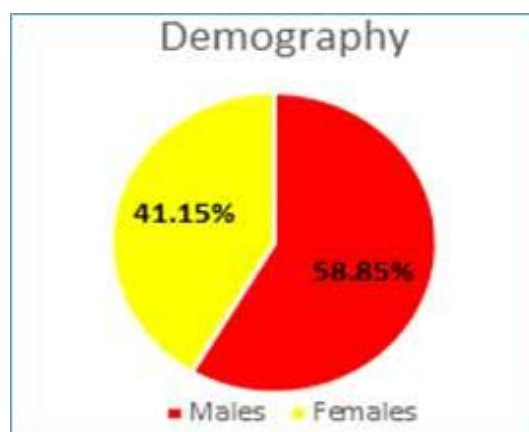


Figure 1

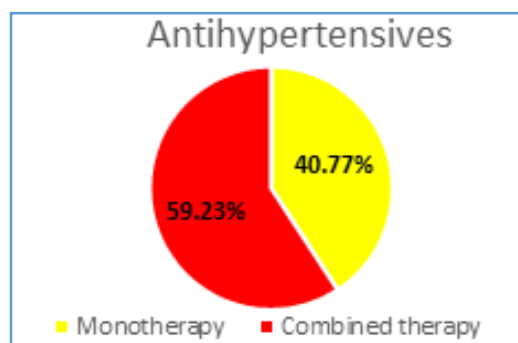


Figure 2

Among monotherapy, ACE inhibitor Enalapril (n=350) and Ca channel blocker Amlodipine (n=332) were the most prescribed drug followed by beta blocker Atenolol (n=166). Among combined drug therapy, only two combinations were

prescribed, dual therapy of Amlodipine with Atenolol and triple drug therapy of Amlodipine, Atenolol and Enalapril. Most of the patients were on triple therapy (n=704) than on dual therapy (n=528). Adverse effects were observed more in patients with combination therapy 623 (62.11%) than patients on monotherapy 380 (37.89%). Among monotherapy, Enalapril was associated with most adverse effects (17.15%) as compared to Amlodipine (13.66%) and Atenolol (7.08%). Triple therapy (37.09%) was associated with more adverse effects as compared to dual therapy (25.02%).

Among monotherapy, the only adverse effect observed with Enalapril was dry cough (n=172), while peripheral oedema (n=69) was most common adverse effect among patients on amlodipine. Dizziness and headache were adverse effects observed in patients on atenolol therapy and on dual therapy of amlodipine and atenolol. Dry cough, dizziness and constipation were more common adverse effects in patients on triple therapy of amlodipine, atenolol and enalapril. (Table 2).

Age	Patients with Adverse Effects		Patients without Adverse Effects		Total
	Male	Female	Male	Female	
<20	5	4	10	12	31
21-30	10	20	34	14	78
31-40	128	130	215	70	543
41-50	178	192	242	136	748
51-60	116	132	162	66	476
61-70	48	34	57	40	179
>70	4	2	15	4	25
<b>Total</b>	<b>489</b>	<b>514</b>	<b>735</b>	<b>342</b>	<b>2080</b>

Table 1

Adverse Effects	Enalapril (n=350)	Amlodipine (n=332)	Atenolol (n=166)	Amlodipine +Atenolol (n=528)	Amlodipine +Atenolol +Enalapril (n=704)
Peripheral oedema		69		10	13
Dry cough	172		06	30	113
Flushing		11			
Headache		14	23	56	22
Dizziness		10	24	120	138
Palpitations		05		05	10
Dyspnoea		04			
Insomnia		05	18	20	20
Abdominal pain		19		10	05
Constipation					51
No Adverse effects	178	195	95	277	332

Table 2

**DISCUSSION**

The overall occurrence of hypertension is similar between both men and women, but differs with age.<sup>13</sup> For those younger than 45 years old, high blood pressure is more common in men than women. For those 65 years old or above, high blood pressure affects women more than men.<sup>14,15</sup> BP values increase with age, and HTN is very common with the elderly. The lifetime risk of developing HTN among those 55 years of age and older who currently have normal BP is 90%.<sup>13,14</sup> For the majority of patients with high blood pressure, the cause is unknown. This is classified as primary or essential HTN. A small portion of patients have a specific cause of their high blood pressure, which is classified as secondary HTN.<sup>13,15,16</sup> Treatment for hypertensive patients includes both non-pharmacologic (lifestyle changes) and pharmacologic (medication) therapy to lower blood pressure and prevent cardiovascular (heart) events such as a heart attack. Implementation of lifestyle interventions should be used throughout the management of all patients with high blood pressure.<sup>13,14</sup> According to the updated 2014 Eighth Joint National Committee (JNC-8) guidelines on HTN, evidence from clinical trials indicate that antihypertensive medications should be initiated in patients less than 60 years old if the systolic blood pressure is persistently >140 mmHg and the

diastolic blood pressure is persistently >90 mmHg despite non-pharmacologic therapy. If the patient's age is 60 or above, antihypertensive therapy should be initiated if the systolic blood pressure is >150 mmHg and the diastolic blood pressure is >90 mmHg.<sup>17,18</sup>

About 35% of hypertensive patients will discontinue their medication within six months,<sup>19</sup> and in at least 50% of cases, the reason for discontinuation relates to adverse effects and patient dissatisfaction.<sup>20</sup> Therefore, it is imperative that hypertension practitioners are fully cognisant of the adverse effects of antihypertensive drugs. Therefore, a study on adverse effects of antihypertensive drugs was undertaken.

The demographic details of our study population showed predominance of adverse effects in females over males, which was similar to that reported in other studies found in the literature.<sup>21,22</sup>

In this study, ACE inhibitor or Calcium channel blocker is the most commonly prescribed antihypertensive drug as monotherapy. According to a study conducted by Nelson C,<sup>23</sup> ACE inhibitors and calcium channel blockers are consistently the most frequently prescribed antihypertensive agents in both younger and older patients with hypertension. It was seen that combined drug therapy was associated with more

adverse effects than monotherapy which was similar to previous studies.<sup>21,22,24</sup> The side effect of dry cough seen with few patients of atenolol and amlodipine combinations is mostly due to atenolol, a selective blocker as demonstrated in the study by Baker<sup>25</sup> that many commercially available selective beta-1 blockers have high affinity for beta-2 receptors. Therefore, both selective and nonselective beta-blockers may cause bronchoconstriction, which can lead some patients to experience a cough reflex. According to this study, occurrence of adverse effect is more common in patients on ACE inhibitor Enalapril than other antihypertensive medications. This result is similar to the study of Gryglas P<sup>26</sup> and Shrestha et al<sup>27</sup> in which more side effects were experienced in Enalapril group than that of Amlodipine. The adverse effect mostly associated with enalapril was dry cough. This is in confirmation of previous reports with almost 44% of patients experiencing dry cough on using ACE inhibitors.<sup>28,29</sup> A dry cough, possibly the result of accumulation of bradykinin in the bronchial mucosa, is the commonest persistent adverse effect. The most common adverse effect seen with amlodipine was peripheral oedema (n=69). Oedema occurs with Ca channel blockers because of vasodilatation in distal arterioles, thereby leading to increased intravascular capillary pressures and increased venous pressures, at least in lower extremities and leakage of fluid into extracellular space. Excessive vasodilatation results in headache, dizziness and flushing.

Present study was a single institutional based so results may not be extrapolated to general population.

#### CONCLUSION

At our tertiary care centre, enalapril and amlodipine were the most commonly prescribed drugs while enalapril was most commonly associated with adverse effects as compared to amlodipine and atenolol. The combination therapy was associated with more adverse effects as compared to monotherapy in the present study. This study setting was institutional based which may not be generalised. However, assessment of adverse effects associated with use of antihypertensive drugs should be done continuously to prevent dropout of treatment and improve patient's adherence to treatment.

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