COMPARATIVE EFFICACY OF AMLODIPINE AND HYDROCHLORTHIAZIDE-AMILORIDE IN CASES OF MILD ESSENTIAL HYPERTENSION IN OUTDOOR PATIENTS AT COMBINED MILITARY HOSPITAL MULTAN

Muhammad Usman Ullah, *Muhammad Babar Khan, **Muhammad Tahir, ***Wasim Alamgir, ****Muhammad Ali Yousaf, *****Asif Hashmat, **Manzoor Qadir

2 Mtn Fd Amb, *MH Rawalpindi, **PAF Hospital Islamabad, ***CMH Multan, ****130 Fd Amb, *****CMH Dera Nawab Sahib,

ABSTRACT

Objectives: To compare antihypertensive effect of fixed dose combination Hydrochlorothiazide-Amiloride and Amlodipine in patients of mild essential hypertension.

Study Design: Randomized controlled trial (RTC)

Place and Duration of Study: Department of Medicine Combined Military Hospital Multan Cantt from 29 January 2007 to 29 June 2007.

Patients and Methods: After fulfilling the inclusion criteria of mild essential hypertension, defined as per recommendations of Seventh Joint National Committee (JNC 7) for treatment of Hypertension as stage 1 hypertension, systolic blood pressure (SBP) ≥ 140-159-mmHg and Diastolic blood pressure(DBP) ≥ 90-99-mmHg, 100 patients were randomized into two study groups using a table of random numbers. Group 1 received tab amlodipine (5 mg) and Group 2 received tab hydrocholrthiazide-amiloride (25 mg-2.5mg). Informed written consent was taken. The patients were followed on subsequent visits (6 in total) for five months and systolic and diastolic blood pressure was recorded carefully. All the data thus obtained were processed and analyzed using SPSS version 10.0. Mean and standard deviation (SD) were calculated for age, diastolic and systolic blood pressure.

Results: In group 1 the drop in mean SBP between first and last visit was 15.42 mm Hg. In group 2 the drop in mean SBP between first and last visit was 18.34 mm Hg. In group 1, the drop in mean DBP between first and last visit was 10.08 mm Hg. In group 2 the drop in mean DBP between first and last visit was 14.65 mmHg. Mean drop in SBP of both the groups were compared with each other and found to be significantly different (P=0.003). Similarly mean drop in DBP of both the groups were compared with each other and found to be significant statistically (P=0.001).

Conclusion: Hydrochlorothiazide-Amiloride had significantly better antihypertensive effect than Amlodipine in patients of mild essential hypertension at the end of five months therapy.

Keywords: Mild essential hypertension, Amlodipine, Hydrochlorothiazide-Amiloride

INTRODUCTION

High blood pressure (BP) is a leading risk factor for heart disease, stroke, and kidney failure [1, 2]. It is estimated that 45 million people in the United States are afflicted with hypertension [3, 4]. So it is not surprising that BP measurement is one of the most common reason for a visit to the doctor [3].

Although there are many antihypertensive medicines available, "thiazide diuretics" have proven to be the gold standard in the treatment of hypertension [2, 5, 6]. Calcium channel blockers (CCBs) enjoy a reputation for efficacy and tolerability [2]. Thiazides are also the lowest priced antihypertensive drugs [7]. Despite this, thiazides are underutilized [2]. Despite its high cost, amlodipine is the largest-selling antihypertensives drug worldwide, both in terms of cost and in terms of dosages [7, 8]. In Pakistan one-month treatment with once daily Hydrochlorothiazide-amiloride (50mg-5mg) would cost Rs 45 only, compared with Rs 690 for Amlodipine (10mg) daily.

Objective

To compare antihypertensive effect of fixed dose combination Hydrochlorothiazide-Amiloride and Amlodipine (Tab amlodipine 5mg and tab hydrocholrthiazide-amiloride 25 mg-2.5mg) in patients of mild essential hypertension.

Correspondence: Maj Muhammad Usman Ullah, Classified Medical Specialist, 2Mtn Field Ambulance
Email: Muhammadusmanullah2009@hotmail.com
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PATIENTS AND METHODS

Operational Definitions

Mild Essential hypertension: Defined (as per recommendations of Seventh Joint National Committee (JNC 7) for treatment of Hypertension) [1] as

Stage 1 Hypertension: Systolic blood pressure ≥ 140-159-mmHg and Diastolic blood pressure ≥ 90-99-mmHg.

Data Collection Procedure

This randomized control trail (RCT) was carried out at Combined Military Hospital Multan. Patients were selected from medical out patient department. The inclusion criteria were male and female patients from 25 to 70 years of age with mild essential hypertension. Written informed consent was taken from the patients. A detailed history and relevant physical examination was carried out. Complete metabolic profile, Electrocardiogram and chest X ray were done in all cases. All patients selected for the study were given a trial of low salt diet and exercise for four weeks to decrease their blood pressure and only those were enrolled in the final study who had persistently high BP and required drug therapy.

These patients were randomly divided into two study groups. Group 1 received Tab Amlodipine (5 mg) and Group 2 receiving Tab Hydrocholrthiazide-Amiloride (25 mg-2.5mg). In total 100 patients were enrolled in the study. Patients were assessed monthly, making total of six visits for each patient in five months. The blood pressure measurement of these patients was carried out on each visit to assess anti hypertensive effect of the two drugs. Subjects were also advised to follow a diet containing low salt and low saturated fat, and moderately high fiber diet along with regular exercises.

Special care was taken for blood pressure measurements of patients i.e.; proper BP machine calibration, positioning of patient, and selection of appropriate cuff size. The BP was taken at least twice on each visit, with an interval of 5 minutes in between. The recorded value on the patient's chart was the average of the last two measurements. The findings of each visit were recorded on a Demographic proforma. The prices of the two drugs and cost of laboratory tests was borne by the hospital authorities as all patients were entitled. The mean systolic and diastolic blood pressure were calculated for each group at 5th month and compared with the base line values.

Data Analysis Procedure

The Data was analyzed using statistical software SPSS version 10.0. Categorical data for male and female was given in percentages. Descriptive statistics were used to calculate mean and standard deviation (SD) for age, systolic and diastolic blood pressures. Mean and standard deviation was calculated for systolic and diastolic blood pressures on each visit. Independent sample T test was applied to compare means of systolic and diastolic blood pressures values of both groups at baseline and at each subsequent visit. Drop in systolic and diastolic blood pressures was calculated between baseline and last visit of treatment. Their mean values were compared among the two treatment groups using independent sample T test.

RESULTS

A total of 100 patients were enrolled initially out of which 94 completed treatments. Two were lost to follow up (one from each group) and four were excluded due to persistently high BP. Both groups had similar baseline characteristics including age, SBP and DBP (Table-1).

The Group 1 of 46 patients, the mean SBP decreased from 154.22mmHg SD± 3.18 to 138.83 (SD± 3.6) at the end of 5 months. The mean DBP decreased from 96.34 mm Hg, SD ± 2.11 to 86.19 (SD±5.66) at the end of 5 months treatment (Table-2 and Fig. 1).

In Group 2 of 48 patients, the mean SBP of 154.82 mmHg SD±2.72 decreased to 136.87 SD±4.6 mmHg. The mean DBP decreased from 96.96 mmHg (SD±1.70) to 82.42 (SD±6.06) in 5 months of treatment (Table - 2 and Fig. 2). The decrease of mean SBP and mean DBP in both the groups at the end of 5 months was found to be statistically significantly different.

DISCUSSION

The objective of treatment in hypertension is to decrease cardiovascular morbidity and

Table-1: Baseline description of patients:

	Group 1 (n = 46)	Group 2 (n = 48)	P values
Age (Years)	56.28 ± 11.34	34.68 ± 10.52	
	154.22 ± 3.18	154.82 ± 2.72	0.31
	96.34 ± 2.11	96.96 ± 1.72	0.10

Table-2: Mean Systolic and Diastolic Blood Pressures of Both Groups (Over Six Months) mmhg n=96

visit	treatment group 1 (amlodipine) (systolic BP diastolic BP)	treatment group 2 (hctz-amiloride) (systolic BP diastolic BP)	p value
VISIT 0	154.22 ± 3.18	154.82±2.72	P=0.31
	96.34 ±2.11	96.96 ±1.70	P=0.10
VISIT 1	151.0 ±5.4	151.87 ±5.3	P=0.43
	94.6 ± 2.5	94.0 ±1.49	P=0.16
VISIT 2	150.15 ±4.9	149.11 ±5.7	P=0.34
	93.49 ±2.47	88.0 ± 3.67	P=0.00
VISIT 3	145.51 ± 4.5	139.83 ±3.7	P=0.00
	92.13 ±2.7	85.26 ±5.9	P=0.00
VISIT 4	142.26 ±3.90	138.33 ±3.9	P=0.00
	89.4 ±3.5	83.81 ±6.1	P=0.00
VISIT 5	138.83 ±3.6	136.87 ±4.6	P=0.00
	86.19 ±5.66	82.42 ±6.06	P=0.00S

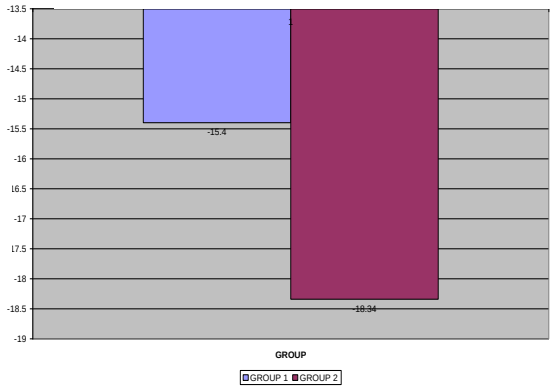

Figure-1: Drop in Mean Systolic BP from Baseline to last visit

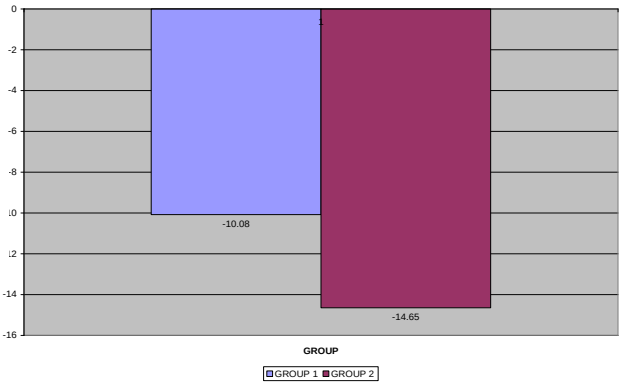

Figure-2: Drop in Mean Diastolic BP from Baseline to last visit

mortality resulting from these diseases [1]. Thiazides are effective antihypertensives, reducing the risk of cardiovascular disease but still underutilized [7]. These drugs are also among the best tolerated antihypertensives [2]. and by far the lowest priced antihypertensive drugs [7]. Consequently, all clinical practice guidelines recommend thiazides as one of the first-line agents [1, 2].

Comparing these drugs only for their antihypertensive efficacy i.e. decreases in BP from baseline was the mainstay of this research. Findings of this study suggest that Hydrochlorothiazide-Amiloride reduced both systolic and diastolic blood pressures significantly as compared to Amlodipine in patients of "Mild Essential Hypertension (JNC stage 1)".

The results of this study are supported by some international studies as well. The results of the largest hypertension trial, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), in which over 30,000 patients with mild to moderate hypertension were randomized to a first-line thiazide-like diuretic, an angiotensin converting enzyme inhibitor (ACEI), or a calcium channel blocker (CCB) and followed for 5 years [5]. Findings from ALLHAT suggest that a low dose thiazide

diuretic in both younger and older patients provides better cardio-protection than an ACE inhibitor or a calcium channel blocker in patients with risk factors for coronary artery disease. Heart failure is increased with first-line CCBs as compared to thiazides or ACEIs. Stroke is reduced with first-line thiazides as compared to ACEIs. BP control and tolerability are better with first-line thiazides as compared to ACEIs. Cost is substantially less for thiazides as compared to beta-blockers, ACEIs, CCBs, alpha blockers, and angiotensin receptor blockers. Thus, all three antihypertensive agents resulted in the same cardiovascular and overall mortality and incidence of nonfatal and fatal myocardial infarction. However, chlorthalidone(thiazide diuretic) provided superior stroke and heart failure protection compared to amlodipine and lisinopril. This superiority likely reflected a greater blood pressure lowering with the diuretic [5, 6].

We only had patients of mild hypertension in our study group (i.e. stage one hypertension as per JNC 7 guidelines) because these patients are usually started late on treatment by physicians [4]. Poor SBP control is at least in part related to physician attitudes because a survey of primary care physicians indicated that three-fourths of them failed to initiate antihypertensive therapy in individuals with SBP of 140 to 159 mm Hg, and most primary care physicians did not pursue control to less than 140 mm Hg [9].

Few studies also showed equal BP reduction with both these drugs. Richard et al compared the effects of Amlodipine , chlorthalidone (thiazide diuretic), and placebo in adults more than 50 years of age with stage 1 isolated systolic hypertension (ISH) and found similar BP reduction for Amlodipine and chlorthalidone, for the treatment of stage 1 ISH during 20 weeks of treatment [10].

Almost one third of our study group comprised of elderly people. The blood pressure reduction was more rapid and more effective with diuretics than with Amlodipine. As shown in the ALLHAT trial preferred first-line drug in most elderly hypertensive patients is a thiazide diuretic [5]. Another advantage of thiazide diuretics in older patients is tendency to reduce urinary calcium excretion, leading to positive calcium balance and decreased rates of bone loss and hip fracture [11].

Our study has proved that low price thiazides are better than costly Amlodipine. Six months treatment would cost the patients Rs 135 for half Tab Hydrochlorothiazide-Amiloride daily. While 5mg of Amlodipine daily for six months will cost Rs 2070. Hydrochlorothiazide-Amiloride is almost 15 times cheaper than Amlodipine. Even the cheapest brand of Amlodipine in market is far costlier than Hydrochlorothiazide-Amiloride. Fretheim and colleagues conducted a study to estimate the potential for savings if thiazides were used as the first choice drug for the management of uncomplicated hypertension [7]. It was conducted in six countries (Canada, France, Germany, Norway, the UK and the US) by comparing this estimate with thiazide prescribing, they calculated the number of people that could switch from more expensive medication to thiazides. This enabled them to estimate the potential drug-cost savings. For Canada, France, Germany, Norway, the UK and the US the estimated potential annual savings were US$13.8 million, US$37.4 million, US$72.2 million, US$10.7 million, US$119.7 million and US$433.6 million, respectively. So, millions of dollars could be saved each year if thiazides were prescribed for hypertension, in place of more expensive drugs. In Pakistan there is increasing pressure to contain our healthcare budgets and a sizeable proportion of this healthcare budgets is used for prescription drugs. Our study can be used in future for changing prescribing practices, by guiding physicians that thiazides in mild hypertension potentially save money and at the same time improve quality.

Limitations

The findings of this study may be viewed with caution because of the limitations of the study that it was carried out on a relatively small outdoor hospital population conducted for only five months. Only “fixed doses” and not multiple dose regimes for both our study groups were used. But the strengths of the

study also lie in its relatively focused group of population studied using international standard protocols and provide us prescribing guidelines for treating mild hypertension.

CONCLUSION

From the findings of the study it is safe to conclude that Hydrochlorothiazide-Amiloride has better antihypertensive effect than Amlodipine in patients of Mild Essential Hypertension.

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