A Prospective, Randomized, Open-label, Comparative Study between Amlodipine and Diltiazem in Non-diabetic Patients of Mild to Moderate Hypertension

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Research Article

Abstract: **Introduction:** In developed countries hypertension is held responsible a fourth contributor to premature death, while it ranks seventh in developing countries. It is important to know this fact because even a 2 mmHg decrease can prevent 151,000 stroke and 153,000 coronary heart disease deaths in our country.Ca^{2+} channel blockers are effective and preferred drugs in lowering blood pressure and decreasing cardiovascular events in the elderly with isolated systolic hypertension. It is therefore imperative that we should have maximum data on their pattern of utilization and the adverse drug reactions. **Aims and Objective:** To observe and compare the anti-hypertensive efficacy as well as incidence of adverse drug reactions between amlodipine anddiltiazem. **Materials and Methods:** This prospective, comparative, open-label study included 80 patients suffering from stage I / II essential hypertension. These patients included males and females randomized in each study group. **Observation and Result:** In the present study, we observed that amlodipine anddiltiazem are effective agents in reducing both systolic and diastolic BP throughout the study period when measured at the 15thday, 30thday, 45thday and 90th day. A total of 39% of the patients reported some sort of adverse-effects like peripheral oedema (12.5%), nausea(5%), dizziness (5%), headache (7.5%) and , abdominal pain (2.5%) in the group1 and 24% in the diltiazem treated group 2, with noted adverse-effects like peripheral oedema (5%), nausea (5%), dizziness (5%), headache (5%) and abdominal pain (0%). **Conclusion:** The antihypertensive effect of these two drugs included in the study was statistically significant. These two drugs were equally effective in reducing the systolic and diastolic blood pressure. The incidence of peripheral oedema, abdominal pain and headache were more in amlodipine treated group than diltiazem treated group. However, this difference in the frequency of adverse-effects between the two groups was not statistically significant ($P >$ 0.05). Adverse effects were tolerated by both the study groups and hence can be used as efficient antihypertensive drugs in management of essential hypertension.

Keywords: Amlodipine, calcium channel blockers, diltiazem, hypertension.

Introduction

Hypertension is one of the major modifiable risk factors for cardiovascular diseases and in most of the cases is not associated with any symptoms. Hypertension being an independent risk factor may be associated with many other coexistent risk factors such as obesity, hyperlipidemia, smoking, diabetes mellitus which compound the risk of cardiovascular diseases (CVD).[1] Various studies have documented the benefits of lowering the blood pressure levels in hypertension in terms of decreased cardiovascular mortality and these benefits occur independently of the specific antihypertensive agent used.[2]In developed countries hypertension is held responsible a fourth contributor to premature death, while it ranks seventh in developing countries.[3]It is important to know this fact because even a 2 mmHg decrease can prevent 151,000 stroke and 153,000 coronary heart disease deaths in our country.[4] Different classes of antihypertensive drugs are used for first line management of uncomplicated hypertension; include thiazide diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers and calcium channel blockers.[1]Despite their similar cardiovascular benefits, antihypertensive agents clearly exhibit distinct adverse effects. Compared with other classes of antihypertensive agents, there is a greater frequency of achieving blood pressure control with Ca^{2+} channel blockers as monotherapy in elderly subjects and in many population groups in which the low renin status is more prevalent. Ca^{2+} channel blockers are effective in lowering blood pressure and decreasing cardiovascular events in the elderly with isolated systolic hypertension. Indeed, these drugs may be a preferred treatment in these patients. Seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high

blood pressure (JNC-VII) gives criteria for defining normal blood pressure, prehypertension, hypertension (stages I and II) and isolated systolic hypertension. Normal blood pressure is when systolic blood pressure <120 mmHg and diastolic < 80 mmHg. Individuals with systolic blood pressure between 120-139 mmHg or diastolic between 80- 89 mmHg are categorised under prehypertension. Prehypertension is not disease category but important to alert clinicians as well as patients to take preventive measures in the form of lifestyle modifications so that they don't develop hypertension. Individuals with systolic blood pressure between 140-159 mmHg and/or diastolic blood pressure between 90-99 mmHg are stratified as having stage 1 hypertension. All individuals levels of systolic blood pressure >/= 160 mmHg and/or diastolic blood pressure >100 mmHg qualify to be put under stage 2 hypertension.[1]

Blood Pressure measurement and diagnosis of hypertension

A well-calibrated sphygmomanometer of adequate size should be used so that the bladder within the cuff encircles at least 80 % of the arm circumference. Blood pressure readings are taken after the patient has been resting comfortably in sitting with feet on the floor or supine position for 5 minutes. One can delay taking measurements up to at least 30 minutes if the patient had smoked or consumed coffee. Two blood pressure recordings at two or more visits with systolic blood pressure >140 mmHg or diastolic blood pressures > 90 mmHg are needed to label a patient hypertensive. But one cannot delay the diagnosis in cases of hypertensive urgency with blood pressure levels>220/125 mmHg with or without end organ damage andhypertensive emergency with evidence of life threatening end-organ damage.[5]While in majority, no cause can be found and are termed to be having primary or essential hypertension.[5]

Calcium Channel Blockers

Ca2+ channel antagonists are important drugs for the treatment of hypertension.

Calcium channel blockers (CCB) are widely used for the treatment of cardiovascular disease, particularly angina pectoris, arrhythmias, and arterial hypertension. Their beneficial effects are related to systemic vasodilation caused by the inhibition of the inward flow of calcium ions through the L-type calcium channels in the cell membrane. Three main classes of CCB are in current use:

1. *The benzothiazepines (diltiazem),*
2. Phenylalkylamines (verapamil), and
3. Dihydropyridines (nifedipine, amlodipine, and others). [6]

Materials and Methods

Study Population

Our study was a prospective, randomized, controlled, open-label, parallel group study in non-diabetic patients of mild to moderate hypertension attending Medicine OPD of a tertiary care hospital. The eligibility criteria for enrolment of the study subjects were as follows:

Inclusion criteria

i. Age: 18 to 75 years, male or female subjects consenting to participate
ii. Mild hypertension (SBP: 140-159 mmHg and/or DBP: 90-99 mmHg)
to Moderate hypertension (SBP: 160-179 mmHg and/or DBP: 100 -109 mmHg)

Exclusion criteria

i. Type 1 diabetes or type 2 diabetes mellitus
ii. History of hypersensitivity to dihydropyridine CCBs, ARBs or β-blockers
iii. Known case of secondary hypertension
iv. Unilateral or bilateral renal artery stenosis, acute or chronic renal failure, Serum creatinine >/= 2.5 mg/dl
v. Known case of COPD or bronchial asthma
vi. Subject is a smoker
vii. Patient with significant ECG abnormality and clinically significant cardiovascular disease
viii. History of hypertensive encephalopathy/ stroke/ transient ischemic attack (TIA) within last 6 months
ix. Pregnant, lactating women, women intending for pregnancy

The patients included in the study were randomized, using lottery method into 2 groups of 40 each to receive following treatments orally:

1. Group 1: Amlodipine
2. Group 2: Diltiazem

Patients were followed up at 15^{th} day after starting the treatment for the safety / tolerance assessment and thereafter, at 15^{th}, 30^{th}, 45^{th} and 90^{th} dayafter starting the treatment for monitoring anti-hypertensive efficacy.

Hematological and biochemical examinations were performed at baseline and end of the study.

Haematological and biochemical examinations included-

- Complete blood picture
- Serum creatine
- Serum electrolytes
- Plasma lipid profile
- Blood sugars

Other investigations included-

- Chest X-ray
- Electrocardiogram

Complete history of the patients was documented, regarding their lifestyle, diet, family etc. Height and weight of the patients were documented to calculate the body mass index and grade and relate the physical status of them. Adverse Events (AEs) if any were documented during the follow-up visit and their causality was assessed using the Naranjo ADR probability scale [7]. Adverse drug reactions, such as, peripheral oedema, dizziness, headache, nausea, abdominal pain, palpitation etc. were documented. Visual rating scale was employed for grading dizziness, nausea, headache, palpitation. To propose a hypothesis, after comparing the incidence of ADRs between the two drugs, namely amlodipine, diltiazem employed the statistical hypothesis test of Student's t-test and ANOVA, to calculate the P-value in terms of significance. Student's t-test was used to compare the blood pressures between 0 day, 15, 30, 45 and 90th day of group 1, group 2. This comparison was done for each group and for each parameter (SBP, DBP) separately. ANOVA was used to compare the antihypertensive efficacy between the two groups-intercomparisons.

Results

Participants: The study population consisted of 80 hypertensive subjects, randomly divided into 2 groups of 40 subjects each: group 1, group 2. It was evident that the number of males in each study group was more than the females. Their mean age was 49.141(±7.79) years; baseline blood pressure (systolic / diastolic) mm Hgwas167 (±7.579)/104.5(±5.03) mm Hg for amlodipine group, 165.75(±6.79)/104.75(±5.05) mm Hg for diltiazem group and body mass index 28.6(±8.25)kg/m^2. The target blood pressure of ≤ 140/ 90 mm Hg was achieved in all subjects by appropriate individualized dose titration. The mean (±SD) blood pressure at end of the study was observed as116.25 (±5.4)/ 80.75(±7.9)mm Hg, as114.25 (±6.3)/ 77.75(±4.22) mm Hg, for amlodipine and diltiazemgroups respectively. The study drugs were tolerated by the majority. It is evident that a majority (43%) of the subjects were in the age range of 51-60 years, whereas, only 17.4% of the population was in the age group of 31-40 years. During the study, two patients dropped out and it was compensated by inclusion of newly diagnosed patients basing on the inclusion and exclusion criteria. Baseline clinical characteristics of patients receiving amlodipine, diltiazem were compared. The groups were similar and comparable as regards systolic BP, diastolic BP and heart rate before treatment.

In The Amlodipine-Treated- Group 1

The mean systolic blood pressure prior to treatment was 167mmHg. After treatment, the systolic BP reduced to 136.25 mmHg, 129.5, 124.75 mmHg and 116.25mmHg at 15thday, 30thday, 45thday and 90th day respectively. The reduction in systolic BP was found to be statistically significant ($P < 0.001$) at 15thday, 30thday, 45thday and 90th day of therapy when compared with the baseline readings. The mean diastolic BP before amlodipine treatment was 104.5mmHg. After treatment, the diastolic BP reduced to 86.25mmHg, 83.25mmHg, 81.25 mmHg and 80.75 mmHg at 15thday, 30thday, 45thday and 90th day respectively. The reduction in diastolic BP was found to be statistically significant ($P < 0.001$) at 15thday, 30thday, 45thday and 90th day of therapy when compared with the baseline readings.

In The Diltiazem-Treated- Group 2

The mean systolic BP prior to treatment was 165.75mmHg. After treatment, the systolic BP reduced to136.25 mmHg, 133mmHg, 125.75mmHg and 114.25 mmHg at 15thday, 30thday, 45thday and 90th day respectively. The reduction in systolic BP was found to be statistically significant ($P < 0.001$) at 15thday, 30thday, 45thday and 90th day of therapy when compared with the baseline readings. The mean diastolic BP before amlodipine treatment was 104.75 mmHg. After treatment, the diastolic BP reduced to 86mmHg, 82.25mmHg, 80.25mmHg and 77.75 mmHg at 15thday, 30thday, 45thday and 90th day respectively. The reduction in diastolic BP was found to be statistically significant ($P < 0.001$) at 15thday, 30thday, 45thday and 90th day of therapy when compared with the baseline readings.

Intergroup comparison was done considering Group 1 as standard group.

Taking amlodipine treated group 1 as standard group, intergroup comparison was done. The 90th day blood pressures were compared between the groups. The mean systolic blood pressure on 90thday of amlodipine treated group 1 was116.25mm Hg and mean diastolic blood pressure was 80.75mm Hg. The mean systolic blood pressure on 90thday of diltiazem treated group 2 was 114.25mm Hg and mean diastolic blood pressure was 77.75mm Hg. The intergroup comparison was done using Student's t test –two sample and Analysis of Variance. Comparison of, 90thday blood pressures [SBP/DBP] of group 1 with 90thday blood pressures [SBP/DBP] of group 2 using t-test, the obtained p-value was P>0.05 which is not significant. Using Analysis of Variance the two groups were compared column wise and the resultant p-value was P>0.05 which is insignificant.

Table 1: Effects of the study drugs: Group 1 amlodipine and Group 2 diltiazem on systolic blood pressure (mm Hg): intra-group analysis

Treatment groups		At different time points			P-value	Test used
		Baseline	**15TH day**	**90TH day**		
Group 1	Mean	167	136.25	116.25	***P < 0.0001	paired t-test
	SD	7.57	4.90	5.4		
Group 2	Mean	165.75	136.25	114.25	*** P< 0.0001	paired t-test
	SD	6.75	4.90	6.35		

Abbreviations: SD- standard deviation, *** - extremely significant, ** - very significant, * - significant, ns- not significant

Table 2: Effects of the study drugs: Group 1 amlodipine and Group 2 diltiazem on systolic blood pressure (mm Hg): inter-group analysis

Time Points	Treatment groups		P-value	Test used
	Group 1 [mean] mm Hg	**Group 2 [mean] mm Hg**		
Baseline	167	165.75	ns P>0.05	t- test
15TH day	136.25	136.25	ns P>0.05	t- test
30TH day	129.5	133	ns P>0.05	t- test
45TH day	124.75	125.75	ns P>0.05	t- test
90TH day	116.25	114.25	ns P>0.05	t- test

Abbreviations:*** - extremely significant, ** - very significant, * - significant, ns- not significant

Table 3: Effects of the study drugs: Group 1 Amlodipine and Group 2 Diltiazem on diastolic blood pressure (mm Hg): intra-group analysis

Treatment Groups		At different time points			P-value	Test used
		Baseline	**15TH day**	**90TH day**		
Group 1	Mean	104.5	86.25	80.75	***P < 0.0001	paired t-test
	SD	5.03	4.90	7.9		
Group 2	Mean	104.75	86	77.75	*** P< 0.0001	paired t-test
	SD	5.05	4.96	4.22		

Abbreviations: SD- standard deviation, *** - extremely significant, ** - very significant, * - significant, ns- not significant

Table 4: Effects of the study drugs: Group 1 amlodipine and Group 2 diltiazem on diastolic blood pressure (mm Hg): intergroup analysis

Time Points	Treatment groups		P-value	Test used
	Group 1 [mean] mm Hg	**Group 2 [mean] mm Hg**		
Baseline	104.5	104.75	ns P>0.05	t- test
15TH day	86.25	86	ns P>0.05	t- test
30TH day	83.25	82.25	ns P>0.05	t- test
45TH day	81.25	80.25	ns P>0.05	t- test
90TH day	80.75	77.75	ns P>0.05	t- test

Abbreviations:*** - extremely significant, ** - very significant, * - significant, ns- not significant

Adverse drug reactions

The safety analysis was performed on all patients who completed the study.The various adverse drug reactions observed in the study subjects were dizziness, peripheral oedema, headache, nausea, abdominal pain. [Table 5]. A total of 39% of the patients reported some sort of adverse-effects like peripheral oedema (12.5%), nausea(5%), dizziness(5%), headache (7.5%) and , abdominal pain (2.5%) in the group1 and 24%in the diltiazem treated group2, with noted adverse-effects like peripheral oedema (5%), nausea(5%), dizziness (5%), headache (5%) and abdominal pain(0%). However, this difference in the frequency of adverse-effects between the groups was not statistically significant ($P > 0.05$).

Table 5: Summary of incidence of all adverse drug reactions observed in the study subjects (n =80)

Adverse Drug Reaction Observed	Group 1 [n=40]	Group 2 [n=40]
Peripheral Oedema	5	2
Nausea	2	2
Headache	3	2
Abdominal Pain	1	0
Dizziness	2	2

Peripheral Oedema

Five subjects on amlodipine (12.5%; 95%CI) and two subjects on diltiazem (5%; 95%CI).Details regarding the intensity of the peripheral oedema and other related features are tabulated in [Table 5]. Peripheraloedema was seen in both male and female in the two groups but females were more affected than males. Peripheral oedema was noticed mostly in ankle and foot bilaterally.

As it was bilateral, girth measurement using inch tape, did not give good significance.

Headache

3 subjects on amlodipine (7.5%incidence; 95%C.I.) andtwo subjects on diltiazem(5%,95%C.I.) had symptoms of headache. Headache was documented based on VRS scale. It was in the range of mild to moderate and did not lead to discontinuation of therapy.

Nausea was seen in two subjects of amlodipine group (5%) andtwo subjects of diltiazemgroup (5%). It was graded as mild in all patients who had symptoms of nausea based on VRS scale.

Dizziness was seen in two subjects of amlodipine group (5%) and two subjects of diltiazemgroup (5%).

Abdominal pain was seen inone subject of amlodipine group (2.5%).

Discussion

Our study was designed to monitor the Efficacy and various adverse drug reactions seen with the Calcium Channels Blockers containing the dihydropyridines namely amlodipine and Benzothiazepines namely diltiazem, with the aim to observe the efficacyand incidence of adverse drug reactions between the two groups.

1. The two groups were comparable to each other in terms of age, weight and baseline characteristics such as sex ratio, smoking and alcohol habits. It is evident that a majority (43%) of the subjects were in the age range of 51-60 years, whereas, only 17.4% of the population was in the age group of 31-40 years.
2. In our study, the mean age of study subjects was 49.141(±7.79) years; baseline blood pressure (systolic / diastolic) mm Hg was167 (±7.579) /104.5(±5.03) mm Hg for amlodipine group, 165.75(±6.79) /104.75(±5.05)mm Hg for diltiazem group and body mass index 27.6 kg/m ^{2}. The target blood pressure of ≤ 140/ 90 mm Hg was achieved in all subjects by appropriate individualized dose titration. The mean (±SD) blood pressure at end of the study was observed as116.25 (±5.4)/ 80.75(±7.9) mm Hg, as114.25 (±6.3)/ 77.75(±4.22) mm Hg for amlodipineand diltiazem, groups respectively. The study drugs were tolerated by the majority.
3. In the present study, we have observed that amlodipine and diltiazem are effective agents in reducing both systolic and diastolic BP throughout the study period when measured at the 15thday, 30thday, 45thday and 90th day.
4. When efficacy was compared, we found that the two drugs were equally effective in reducing the systolic and diastolic blood pressure.
5. Our findings indicated that the incidence of nausea was 2% with amlodipine, when compared to diltiazem (2%).
6. Our findings indicated that the incidence of abdominal pain was amlodipine1%, when compared to diltiazem (0%).
7. The incidence of dizziness in this study was amlodipine2% anddiltiazem2%.
8. The incidence of headache in this study was amlodipine3% anddiltiazem 2%.
9. The changes in laboratory parameters were minor and of no clinical relevance. As in previous studies change in plasma glucose and lipid values was slight with calcium channel blockers. [8]
10. Lower extremity oedema was observed in five subjects on amlodipine (12.5%; 95%CI), two subjects on diltiazem (5%; 95%CI). In a literature survey lower extremity edema was a unique adverse effect ofcalcium channel blockers that warrant further discussion.[9,10]
11. In our study,heart rate was slightly higher in the diltiazem group than amlodipine group but this difference was not significant [11].

Summary and Conclusion

In this study, the efficacy and adverse effects of amlodipine, diltiazem in essential [stageI/II] hypertensive patients was observed.

1. The study population consisted of 80 hypertensive subjects, randomly divided into 2 groups of 40 subjects each: group 1 and group 2. The number of males in each study group was more than the females. Their mean age was 49.141(±7.79) years.
2. Baseline blood pressure (systolic / diastolic) mm Hg was167 (±7.579) /104.5(±5.03) mm Hg for amlodipine group, 165.75(±6.79) /104.75(±5.05) mm Hg for diltiazem group and body mass index 27.6 kg/m ^{2}. The target blood pressure of ≤ 140/ 90 mm Hg was achieved in all subjects by appropriate individualized dose titration.
3. The mean (±SD) blood pressure at end of the study was observed as116.25 (±5.4)/ 80.75(±7.9) mm Hg, as114.25 (±6.3)/ 77.75(±4.22) mm Hg for amlodipine and diltiazemgroups respectively.
4. A total of 39% of the patients reported some sort of adverse-effects like peripheral oedema (12.5%), nausea(5%), dizziness (5%), headache (7.5%) and abdominal pain (2.5%) in the amlodipine treated group1 .
5. A total of 24%of the patients reported some sort of adverse-effects like peripheral oedema (5%), nausea (5%), dizziness (5%), headache (5%) and

abdominal pain (0%)in the diltiazem treated group 2.

The antihypertensive effect of the two drugs included in the study was statistically significant. Though amlodipine anddiltiazemhad adverse effects, they were tolerated by the patients and hence can be used as efficient antihypertensive drugs in management of essential hypertension.

References

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al;Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 2003; 42(6):1206-52.
2. Blackburn DF, Wilson TW. Antihypertensive medications and blood sugar: theories and implications. Can J Cardiol 2006; 22(3):229-33.
3. Pradeepa R, Mohan V. Hypertension andpre-hypertension in developing countries Indian J Med Res 2008; 128:688-90.
4. Rodgers A, Lawes C, MacMahon S. Reducing the global burden of blood pressure related cardiovascular disease. J Hypertens 2000; 18(Suppl 1): S3–S6.
5. Sutters M. Systemic Hypertension. In: McPhee SJ, Papadakis MA, Rabow MW, editors. Current Medical Diagnosis and Treatment. 50th ed. USA: McGraw Hill Lange; 2011.p.416-45.
6. British Hypertension Society, G:\Website\Drug Classes\Drug Classes Final Copy Dec 2008\Calcium Channel Blockers.doc.
7. Naranjo et.al. ClinPharmacolTher. 1981 Aug;30(2):239-45.
8. Clinical acceptability of therapy ofACE inhibitors in mild to moderate hypertension, a comparison between perindopril and enalapril . Alcocer L., C. Campos, Bahena JH, Nacaud A., Parra J Carrillo., C. Calvo, C.Weber, G. LereboursMickalonis L., Villahermosa Cardiovasc Drug Ther Mt 1995, 9:431-436.
9. Dougall HT, McLay J (1996) A comparative review of the adverse effects of calcium antagonists. Drug Safety 15:91–106.
10. Meraw SJ, Sheridan PJ (1998) Medically induced gingival hyperplasia. Mayo ClinProc 73:1196–1199
11. Bertorini TE, Palmieri GM, Griffin JW, Igarashi M, McGeeJ, Brown R, Nutting DF, Hinton AB, Karas JG (1988) Effectof chronic treatment with the calcium antagonist diltiazem induchenne muscular dystrophy. Neurology 38:609–613.