

A Comparative Clinical Trial of Efonidipine and Amlodipine in Management of Stage-I Hypertension: A Randomized, Double Blind Study in Indian Population

ABSTRACT

Aims: The present clinical study was conducted to establish non-inferiority of efonidipine hydrochloride ethanolate (efonidipine) as compared to amlodipine besylate (amlodipine) in the management of Stage I hypertension.

Study design: The study was a prospective, cohort, double-blind, double-dummy, randomized phase-III clinical trial

Place and Duration of Study: Nine geographically distributed sites across India were involved in the clinical trial between January 2015 to June 2016

Background- The use of conventional L-type CCBs is often limited due to associated side effects. Efonidipine, a dual T- and L-type Ca^{2+} channel blocker has been proven to exhibit antihypertensive effect along with renoprotective actions with minimum systemic side effects. The present clinical study was conducted to evaluate the safety and efficacy of Efonidipine for the first time on Indian patients with Stage-I hypertension.

Methodology - The present phase-III clinical trial was a double-blind, double-dummy, multi-center, and parallel group study conducted on Indian population. A total of 200 patients were randomized to receive either efonidipine 40mg (n=95) or amlodipine 5mg (n=105) once daily for 28 days. The patients were evaluated for changes in the systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate.

Results- Efonidipine reduced SBP by 18.2 ± 12.2 mmHg, DBP by 10.7 ± 7.0 mmHg and heart rate was diminished by 8.1 ± 8.3 bpm while amlodipine reduced SBP by 19.2 ± 11.8 mmHg, DBP by 10.2 ± 7.7 mmHg and heart rate by 7.2 ± 9.9 bpm.

Conclusion- Efonidipine was concluded to be non-inferior to amlodipine in reduction of SBD, DBP and heart rate and was found to be comparable to amlodipine in management of hypertension and its safety profile.

Clinical Trial Registration- The trial was registered with the Clinical Trial Registry of India; Reg. No: CTRI/2015/01/005359; Available at:

<http://ctri.nic.in/Clinicaltrials/showallp.php?mid1=7747&EncHid=&userName=CTRI/2015/01/005359>

Keywords: Efonidipine, Hypertension, Renoprotection, T-type Ca^{2+} channel, Dihydropyridines

1. INTRODUCTION

Hypertension is a multifactorial and multifaceted disease which can lead to organ dysfunction. There is a close relationship between blood pressure levels and the risk of cardiovascular events, haemorrhagic strokes, and kidney disease (1). A growing body of accumulated evidence has proven that antihypertensive therapy provides substantial benefit in reducing the incidence of cardiovascular diseases and assists in curbing the progress of renal damage (2, 3).

Therapeutic potential of calcium channel blockers (CCBs) is well established in the treatment of a wide range of cardiovascular disorders such as hypertension, angina pectoris and arrhythmia. Additionally, conventional CCBs have been reported to cause an increase in glomerular filtration rate (GFR) and hence are preferred to be prescribed to hypertensive patients with renal impairment (4). Dihydropyridines (DHPs) are among the most widely used CCBs for the management of cardiovascular disease (5).

Voltage-sensitive calcium (Ca^{2+}) channels have been classified into five types (L-, P/Q-, N-, R-, and T-type) based on their localization and functions(6). Conventional dihydropyridines (DHPs) act mainly on L-

type Ca^{2+} channels (7) with a few compounds exhibiting dual blocking action on the L-type and T-type Ca^{2+} channels (8). Therapeutic use of L-type CCBs is often limited as they cause unwanted side effects like ankle oedema, headache, flush etc and they are often accompanied with reflex tachycardia (9). T-type Ca^{2+} channels are expressed all through the body, including heart, kidney, nervous tissue, smooth muscles, and endocrine organs. They have more negative voltage range of activation and inactivation and rapid gating kinetics as compared to L-type Ca^{2+} channels, and are hence resistant to conventional CCBs (8). Blocking of T-type Ca^{2+} channel for the treatment of various cardiovascular disorders has been proven beneficial as it participates in cardiac pacemaking, regulation of vascular tone and hormone secretion (10). Blockade of T-type Ca^{2+} channel is associated with minimum reflex tachycardia and enhanced renal protection (8) as the blocking causes dilatation of both afferent and efferent renal glomerular arterioles as well as decrease in plasma aldosterone concentrations (11) (4).

Efonidipine antagonizes both T- and L-type Ca^{2+} channels and like other dihydropyridine CCBs, it was developed as a drug with slow onset and long duration of action (8). It has been clinically used in Japan as an antihypertensive and antianginal agent. Efonidipine reduces blood pressure and heart rate without suppressing myocardial contraction. It has demonstrated potent negative chronotropic effects on isolated right atria (12). Additionally, it increases the glomerular filtration rate without increasing intra-glomerular pressure unlike cilnidipine as it dilates both afferent and efferent arterioles (13). In healthy humans, efonidipine has also shown to decrease plasma aldosterone (ALD) concentration through the blockade of T-type Ca^{2+} channels (11). The degree of renal protection by efonidipine was found to be comparable to that produced by angiotensin converting enzyme inhibitors in hypertensive patients with renal complications (14).

Considering the benefits, a randomized, double-blind, double-dummy, multi-center, and parallel group clinical study with non inferiority design was planned to assess the efficacy and safety of efonidipine hydrochloride ethanolate (efonidipine) as compared to amlodipine besylate (amlodipine).

2. MATERIAL AND METHODS

The study was a prospective, cohort, double-blind, double-dummy, randomized clinical trial and was conducted at 9 different centers geographically distributed across India: 1. Dr. Girish Rajadhyaksha- BYL Nair Charitable Hospital, Mumbai; 2. Dr. Atul Patil- Shree Saibaba Heart Institute and Research Centre, Nasik; 3. Dr. Jitendra Kodilkar- MVP Samaj's Dr. Vasantrao Pawar Medical College, Hospital & Research Centre, Nasik; 4. Dr. Gourango Sarkar- IPGME&R, Kolkata; 5. Dr. Nakul Sinha- Divine Heart & Multispeciality Hospital, Lucknow; 6. Dr. Srinivas Reddy- King George Hospital, Visakhapatnam; 7. Dr. Sanjay Sharma- Omega Hospital, Mangalore; 8. Dr. BLN Prasad- Rajiv Gandhi Institute of Medical Sciences, Srikakulam; and 9. Dr. Akula Siva Prasad- Nizam Institute of Medical Sciences, Hyderabad. The total duration of the treatment phase was 35 days (5 weeks) including 7 days (1 week) washout period and 28 days (4 weeks) of treatment period. The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice (ICH-GCP) guidelines, and Indian regulatory guidelines for conducting clinical trials (Schedule-Y). The study medication and the trial supplies were sponsored by Zuventus Healthcare Ltd. The study monitoring and site management was done by Genelife Clinical Research Pvt. Ltd. The study was initiated after receiving approval from the Drug Controller General of India (DCGI) and the respective institutional ethics committees (IECs) at each of the study centers. Written informed consent was obtained from all patients after thorough explanation of the protocol and the drug related information before participation in the study. The trial was registered with the Clinical Trial Registry of India (Reg. No: CTRI/2015/01/005359).

The eligibility criteria for the patients to be enrolled in the study included the following: Patients aged 18 to 65 years with stage 1 hypertension as per Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII), and heart rate of >83 beats/min. Patients with any of the following criteria were not enrolled in the study: sitting systolic BP ≥ 180 mm Hg, history of stroke or myocardial infarction in the previous 6 months, congestive heart failure, sick sinus syndrome or sinus bradycardia (<50 beats/min), second- or third-degree atrioventricular block, hypersensitivity to dihydropyridine CCBs, hepatic disease with aspartate aminotransferase (AST) or alanine

aminotransferase (ALT) levels >2 times the upper normal limit, renal disease with a serum creatinine concentration >2.0 mg/dL, uncontrolled diabetes with glycosylated hemoglobin A1C (Hb A₁C) >9gm%, renal artery stenosis, or secondary hypertension, pregnant women or nursing mothers, alcohol dependence or abuse, drug abuse, history of chronic smoking (more than 10 units per day of cigarettes, bidis, or any other form), scheduled for surgery anytime during the study, patient receiving some other drug that could possibly alter the bioavailability of the study medication and participation in any other clinical trial within the last month.

Eligible patients maintained on any other antihypertensive, had to undergo a washout period of 1 week before receiving the study medication. Patients were randomized (1:1) to receive either efonidipine 40 mg or amlodipine 5 mg o.d. for a period of 28 days (4 weeks) along with matched placebo of the respective comparator drugs. Computer generated simple block randomization chart was used to randomize the eligible patients. Patients were instructed to take both the tablets once daily in the evening after food in accordance with the prescribing information. Study medications were labeled to ensure that both the patient and the investigator were blinded to the treatment allocation.

The primary objective of the study was to assess the comparative efficacy of efonidipine hydrochloride ethanolate 40 mg and amlodipine besylate 5mg given once daily orally in treatment of hypertension. The secondary objective was to compare the two treatments in terms of safety. The efficacy of both treatments was assessed based on the changes in the systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate at each follow up visit (Day 21 and Day 35) from baseline (Day 7). Clinical signs like Dyspnea and palpitation were assessed using a 4 point Likert type scale from 0 to 3 [0: Absent, 1: Mild (Occurs 1-3 times/week), 2: Moderate (Occurs 4-6 times/week), 3: Intense (Occurs daily)]. Safety assessments included clinical or laboratory adverse events reported during the study period. Adverse events were documented based on spontaneous reporting and investigator's assessment at each visit.

2.1 Sample Size Determination

Sample size for the study was calculated using WINPEPI software at a level of significance of 5% ($\alpha=.05$) and a power of 80% ($\beta=.02$), confidence level of 95%; acceptable difference of .10 and Assumed proportion of .50. The calculated sample size was 97 subjects in each group.

For the present study a total of 200 patients were planned to be recruited, with 100 patients in each group.

2.2 Statistical Analysis

The demographic data was analyzed descriptively and values were expressed as mean \pm standard deviation (SD). All outcome indicators were analyzed with respect to the change in value from the baseline using paired Student's t test. Comparisons between treatment groups were analyzed using unpaired Student's t test and the statistical significance at $P = .05$. Efficacy analysis was performed on the intention-to-treat (ITT) population, which included all patients who were randomized to receive at least one dose of either of the study medications and had available efficacy data at least at one observation after the baseline.

3. RESULTS AND DISCUSSION

3.1 Study Population

A total of 221 patients were screened, out of which 211 patients with Stage I hypertension were enrolled in the study. After the completion of washout period, 11 patients dropped out and 200 patients received the study medication as per the randomization. Out of these, 105 were assigned to amlodipine and 95 were assigned to efonidipine treatment groups (Fig 1). The demographic characters, SBP, DBP, and heart rate of the two groups were statistically similar at baseline (Table 1).

Table 1. Demography and Baseline Parameters

Characteristic	Efonidipine (N=95)	Amlodipine (N=105)	P Value
Age (year)	46.1 ± 13.0	46.6 ± 12.5	.76*
Height (cm)	161.4 ± 8.2	162.2 ± 8.3	.48*
Weight (kg)	66.7 ± 10.9	65.4 ± 10.7	.40*
Gender (%)			
Female	36.8% (n=35)	29.5% (n=31)	.27#
Male	63.2% (n=60)	70.5% (n=74)	
Blood Pressure (mm Hg)			
SBP	149.3 ± 10.0	149.8 ± 10.1	.74*
DBP	91.9 ± 5.4	91.91 ± 5.5	.98*
Heart Rate (bpm)	89.1 ± 5.4	88.62 ± 4.6	.52*

*Pearson's Chi-squared Test; # Unpaired t-test

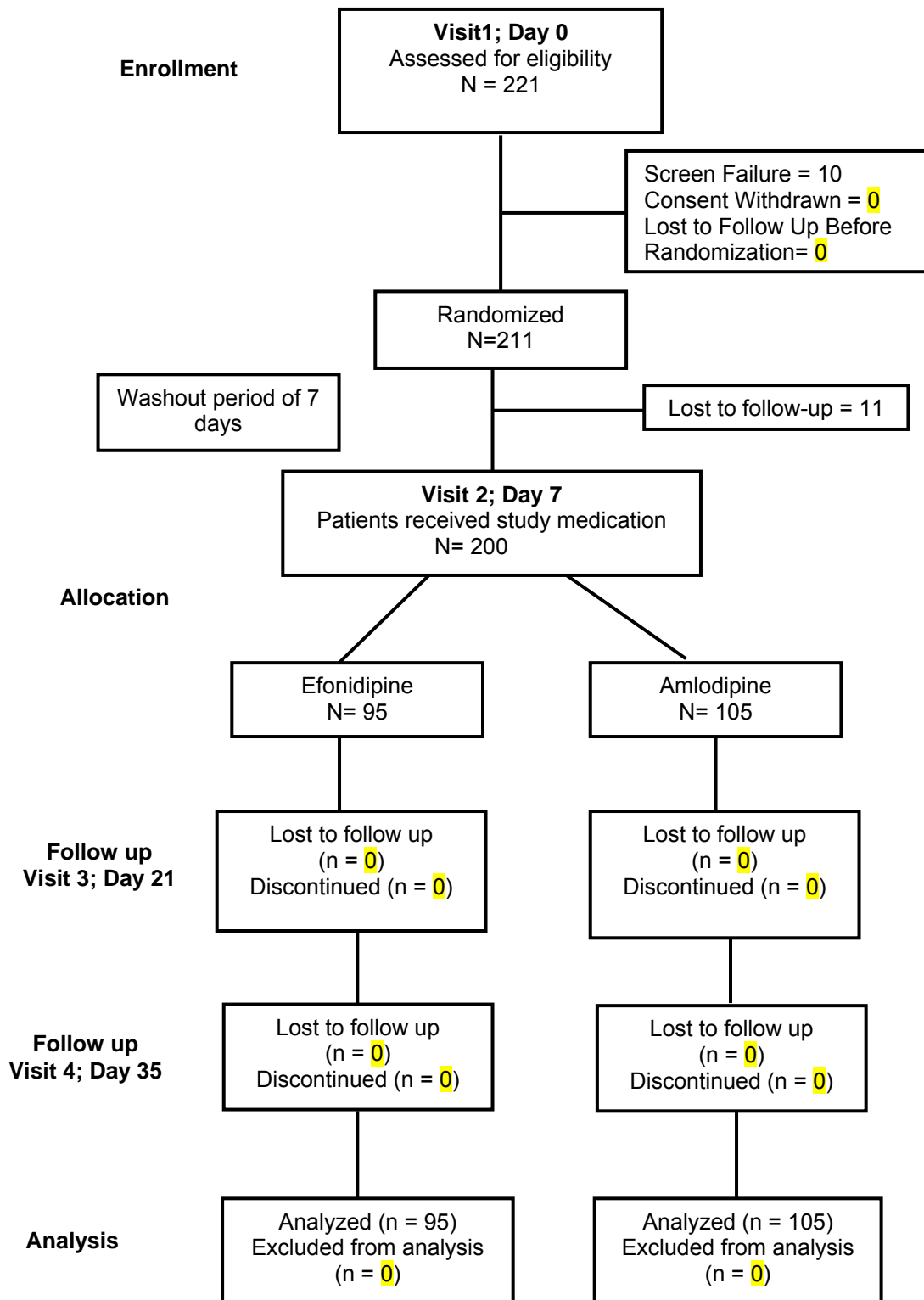


Fig. 1. CONSORT Flow Diagram

3.2 Efficacy

3.2.1 Reduction in blood pressure

Efonidipine and amlodipine after 4 weeks of therapy showed similar improvement in blood pressure (Table 2). Both the groups showed a significant reduction in the blood pressure as compared to the baseline ($P < .001$). Efonidipine reduced mean SBP by 18.2 ± 12.2 mmHg and DBP by 10.7 ± 7.0 mmHg while amlodipine reduced mean SBP by 19.2 ± 11.8 mmHg and DBP by 10.2 ± 7.7 mmHg. On comparing the two groups using unpaired t-test, efonidipine was found to be non-inferior to amlodipine ($P = .54$ for SBP, $P = .57$ for DBP)

Table 2. Changes in Blood Pressure from baseline

	Efonidipine (N=95)		Amlodipine (N=105)	
	SBP (Mean mm Hg ± S.D.)	DBP (Mean mm Hg ± S.D.)	SBP (Mean mm Hg ± S.D.)	DBP (Mean mm Hg ± S.D.)
Visit 2 (Day 7, Baseline)	150.3 ± 7.8	92.6 ± 5.1	149.7 ± 8.6	92.2 ± 5.1
Visit 4 (Day 35)	132.1 ± 11.4	81.8 ± 6.4	130.4 ± 9.7	82.0 ± 6.5
Mean Difference	18.2 ± 12.2	10.7 ± 7.0	19.2 ± 11.8	10.2 ± 7.7
Change from baseline *P	<.001	<.001	<.001	<.001
95% CI	-20.7 to -15.7	-20.7 to -15.7	-21.5 to -17.0	-11.6 to -8.7
SBP- Efonidipine vs. Amlodipine	#P=.54; (95% CI = -4.4 to 2.3)			
DBP- Efonidipine vs. Amlodipine	#P=.57; (95% CI =-1.5 to 2.7)			
*Paired t-test; #Unpaired t-test				

Additionally, it was noted that by the end of the treatment there were 64 (67.37%) patients from efonidipine group and 75 (71.43%) patients from amlodipine group achieved the target JNC VII BP <140/90 mm Hg ($P = .53$) which is statistically not significant for the two groups comparison. On comparing the two treatment arms using Pearson's Chi-squared test for proportion of patients achieving the target JNC VII BP of <140/90 mm Hg, the efficacy of the two treatments was observed to be comparable (Table 3).

Table 3. Patients achieving JNC VII target BP at the end of the study

	Visit 4 (Day 35) No. of patients
Efonidipine (N=95)	64 (67.4%)
Amlodipine (N=105)	75 (71.4%)
P (Pearson's Chi-squared Test)	.53

3.2.2 Heart rate

The mean change in the resting heart rate from baseline was analyzed in the ITT population at each of the follow up visits. The mean heart rate reduced to 80.6 ± 6.8 bpm from 88.7 ± 5.9 bpm in patients treated with efonidipine. In amlodipine group, baseline heart rate of 87.2 ± 8.4 bpm decreased to 79.9 ± 5.8 bpm. A significant change was observed in both the groups as compared to the baseline values (P

<.001). At the end of the treatment phase, efonidipine was found to be non-inferior to amlodipine in reducing heart rate ($P=.48$) (Table 4).

Table 4. Changes in Heart Rate

	Efonidipine (N=95)	Amlodipine (N=105)
Visit 2 (Day 0; Baseline) bpm; Mean ± S.D.	88.7 ± 5.9	87.2 ± 8.4
Visit 3 (Day 21) bpm; Mean ± S.D.	84.3 ± 7.2	82.3 ± 6.4
	* <i>P</i> < .001	* <i>P</i> < .001
	95% CI = -5.8 to -3.1	95% CI = -6.6 to -3.2
	Mean Difference = 4.9 ± 8.8	Mean Difference = 4.4 ± 6.7
Visit 4 (Day 35) bpm; Mean ± S.D.	80.6 ± 6.8	79.9 ± 5.8
	* <i>P</i> < .001	* <i>P</i> < .001
	95% CI = -9.8 to -6.5	95% CI = -9.1 to -5.3
	Mean Difference = 8.1 ± 8.3	Mean Difference = 7.2 ± 9.9
Amlodipine vs. Efonidipine (Visit 4)	# <i>P</i> = .48; NS 95% CI = -1.6 to 3.5	
*Paired <i>t</i> -test; #Unpaired <i>t</i> -test		

As per Framingham Heart study, an average resting heart rate of <83 beats per minute is considered to be ideal as it is associated with lower risk of cardiovascular events (15). The number of patients achieving the target heart rate of <83 bpm was analyzed at the end of the treatment. It was observed that 66.32% patients from efonidipine group and 72.38% patients from amlodipine group achieved the target heart rate by the end of the treatment. No significant difference ($P=.35$) was observed in the proportion of patients achieving the targeted heart rate between the two treatment groups (Table 5).

Table 5. Patients achieving target Heart rate at the end of the study

Treatment Groups	Visit 4 (Day 35)
Efonidipine (N=95)	63 (66.3%)
Amlodipine (N=105)	76 (72.4%)
<i>P</i> (Pearson's Chi-squared Test)	.35

3.2.3 Clinical symptoms of Dyspnea and Palpitation

Improvement in the clinical symptoms of dyspnea and palpitation was evaluated by determining the number of patients whose symptoms were completely resolved by the end of the study. On comparing the two treatment groups, no statistically significant difference was observed between the groups for resolution of dyspnea and palpitation (Table 6).

Table 6. Dyspnea and Palpitation: No. of patients experiencing the clinical symptoms

Treatment Groups	Dyspnea			Palpitation		
	Visit 2 (Baseline; Day 7)	Visit 3 (Day 21)	Visit 4 (Day 35)	Visit 2 (Baseline; Day 7)	Visit 3 (Day 21)	Visit 4 (Day 35)
Efonidipine (N=95)	20	17	4	24	12	6
Amlodipine (N=105)	30	19	6	28	16	11
Efonidipine vs. Amlodipine (Day 35)	$P > .99^*$			$P = .28^\#$		

**- Fisher's Exact test; #-Pearson's Chi-squared Test*

3.3 Clinical Laboratory Tests

Clinical laboratory parameters namely hemoglobin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine, blood urea, total WBC count, platelet count, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides were assessed at the beginning of the study (Visit 1; baseline) and at the last visit (Visit 4; day 28). The changes in the observed values of the parameters have been represented in Table 7.

Table 7. Changes in Clinical Laboratory Parameters

Efonidipine (n=95)	Hemoglobin (mg/dL)	AST (IU/L)	ALT (IU/L)	Serum Creatinine (mg/dL)	Blood Urea (mg/dL)	Total WBC Count (cu.mm)	Platelet Count (x 10⁹/L)	HDL (mg/dL)	LDL (mg/dL)	Triglycerides (mg/dL)
Baseline; Visit 1 (Mean ± SD)	12.9 ± 1.8	31.2 ± 8.9	32.3 ± 13.0	1.1 ± 0.3	25.5 ± 12.2	7444.8 ± 1746.8	256.8 ± 63.8	47.2 ± 9.6	117.2 ± 31.4	139.9 ± 55.4
Day 28; Visit 4 (Mean ± SD)	13.1 ± 1.7	31.9 ± 11.0	34.3 ± 18.8	1.0 ± 0.2	24.1 ± 11.3	7467.1 ± 1634.9	267.1 ± 66.4	48.1 ± 10.4	112.6 ± 30.2	133.1 ± 53.3
Within the group comparison Mean Change from baseline (95% CI), p	0.2 (-1.9 to 1.5) *P=.059	0.7 (-2.6 to 1.2) *P=.47	2.0 (-4.7 to 0.6) *P=.12	-0.1 (0.0 to 0.1) *P=.003	-1.4 (0.2 to 2.6) *P=.03	22.2 (-284.9 to 240.4) *P=.87	-10.3 (-93.8 to 73.1) *P=.01	0.9 (-2.6 to 0.7) *P=.27	-4.6 (-10.5 to 1.3) *P=.13	-6.8 (-2.2 to 15.7) *P=.14
Amlodipine (n=105)	Hemoglobin (mg/dL)	AST (IU/L)	ALT (IU/L)	Serum Creatinine (mg/dL)	Blood Urea (mg/dL)	Total WBC Count (cu.mm)	Platelet Count (x 10⁹/L)	HDL (mg/dL)	LDL (mg/dL)	Triglycerides (mg/dL)
Baseline; Visit 1 (Mean ± SD)	13.2 ± 1.4	30.6 ± 11.7	31.0 ± 13.9	1.0 ± 0.2	24.1 ± 11.3	7148 ± 1711.3	255.3 ± 67.1	50.0 ± 14.9	108.2 ± 29.5	135.4 ± 51.0
Day 28; Visit 4 (Mean ± SD)	13.3 ± 1.4	31.8 ± 9.4	31.0 ± 13.1	0.9 ± 0.2	24.2 ± 11.0	7390.4 ± 1796.9	262.5 ± 66.3	48.1 ± 10.4	107.0 ± 29.5	133.9 ± 46.2
Within the group comparison Mean Change from baseline (95% CI), p	0.1 (-1.6 to 1.4) *P=.21	1.2 (-2.7 to 0.4) *P=.14	0.0 (-1.6 to 1.6) *P=.97	0.0 (-0.0 to 0.1) *P=.08	0.1 (-1.1 to 0.9) *P=.84	242.4 (-475.2 to - 9.6) *P=.04	-7.2 (-96.8 to 82.5) *P=.11	-1.9 (-0.4 to 4.2) *P=.10	-1.2 (-2.7 to 5.1) *P=.53	-1.5 (-4.9 to 7.9) *P=.65
Between the group comparison Efonidipine vs. Amlodipine Visit 4 Mean Change (95% CI), p	0.1 (-0.6 to 0.2) #P=.39	-0.5 (-2.8 to 3.0) #P=.95	2.0 (-1.2 to 7.9) #P=.14	-0.1 (-0.0 to 0.1) #P=.17	-1.5 (-3.1 to 3.1) #P=.99	-220.2 (-404.1 to 557.5) #P=.75	-3.2 (-13.8 to 23.2) #P=.62	2.8 (-2.9 to 2.9) #P=.97	-3.4 (-2.3 to 13.6) #P=.17	-5.3 (-14.7 to 13.0) #P=.90
*Paired t-test; #Unpaired t-test										

3.4 Safety Evaluation

Safety assessments were made at the end of week 2 and 4 after the start of treatment (N=200). Adverse events were reported in 16 subjects (15.23%) in amlodipine group and in 11 subjects (11.57%) in efonidipine group at the end of study. There was no statistically significant difference ($P = .68$) in the number of adverse events reported between the groups. The summary of the adverse events observed during the study is listed in Table 8a.

All these adverse events were mild and resolved without any clinical intervention. The patients were followed up regularly until adverse events were completely resolved. No serious adverse events were reported during the study.

Table 8a. Proportion of patients experiencing Adverse Events

	Visit 3; Day 21 (n=42)		Visit 4; Day 35 (n=28)	
Efonidipine (N=95)	22 (25.2%)	*P =.48; NS	11 (11.6%)	*P =.45; NS
Amlodipine (N=105)	20 (19.0%)		16 (15.2%)	
*Pearson's Chi-squared Test				

Table 8b. Adverse Events: Frequency table

Sr. No.	System Organ Class	Adverse Event	Amlodipine (N = 105)		Efonidipine (N = 95)	
			Visit 3; Day 21	Visit 4; Day 35	Visit 3; Day 21	Visit 4; Day 35
1.	Nervous System Disorder	Drowsiness	6	0	3	1
		Headache	3	7	2	3
2.	General disorders and administration site conditions	Fever	1	1	1	0
		Neck Swelling	0	0	1	0
		Bilateral Pedal Oedema	1	1	0	0
		Body Pain	2	0	0	1
3.	Gastrointestinal disorders	Constipation	1	0	1	0
		Nausea	5	3	9	5
		Gases	0	0	1	0
		Vomiting	0	3	3	0
		Abdominal Pain	1	1	2	1
4.	Respiratory, thoracic and mediastinal disorders	Throat pain	0	0	1	0
Total Number of Adverse events			20	16	24	11

Pedal oedema is a common adverse event associated with amlodipine therapy. The rate of incidence of pedal oedema with conventional CCB use has been reported to be up to 70% which is drug and dose-dependent (16). Since it was a short-term study, one case of pedal oedema was reported in the amlodipine group. A longer duration study is recommended to evaluate the incidence of pedal oedema in Indian population.

3.4 Discussion

Hypertension is a manageable disease which contributes significantly to the overall morbidity and mortality of the general population. It increases the risk of other cardiovascular and renal maladies such as stroke, myocardial infarction, renal impairment, etc., if left uncontrolled. Appropriate pharmacological interventions as a result will reduce the risk of associated cardiovascular and renal events and contribute to a better quality of life (17).

Amongst the front runners in antihypertensive therapy are CCBs. JNC 8 Hypertension guideline algorithm recommends Calcium channel blockers as initial drugs of choice for hypertension (18). Influx of the calcium in vascular smooth muscle cells is inhibited by CCBs causing vasodilatation and lowering of raised blood pressure (19). A major reason for non-compliance with CCBs is the high incidence of peripheral oedema which is a result of their inherent natriuretic property (20). The frequency of incidence of peripheral oedema ranges from 5% to up to 70% (16) (21). Also, therapy with conventional L-type CCBs is accompanied by reflex tachycardia due to their vasodilatory effect (22). The L-type CCBs fail to restrict the renal impairment effectively as they increase the glomerular filtration rate resulting in elevated filtration fraction (13). The filtration fraction, which approximately parallels the changes in intraglomerular pressure, increases with an L-type CCB, does not change with an N-type CCB, and decreases with a T-type CCBs (4).

T-type Ca^{2+} channels which are expressed all over the body have been proven to participate in various pathophysiological pathways (8) (10). T-type Ca^{2+} channel blockers have a distinct advantage in treatment of hypertensive patients with diabetes and/or renal impairment. Efonidipine a dihydropyridine (DHP) CCB blocks both L- and T-type Ca^{2+} channels. Apart from being a potent antihypertensive, the additional T-type Ca^{2+} channel inhibition by efonidipine is responsible for negative chronotropic, renoprotective and cardioprotective effects (23).

Efonidipine like other DHP CCBs exerts its antihypertensive effect by blocking the L-type Ca^{2+} channel thereby inactivating the actin-myosin ATPase activity resulting in decrease of elevated blood pressure (24) (7). Efonidipine was observed to achieve antihypertensive and antianginal effect similar to those produced by other CCBs without any cases of reflex tachycardia (7). The present clinical study was conducted with an aim to establish non-inferiority of efonidipine hydrochloride ethanolate as compared to amlodipine besylate in the management of Stage I hypertension for a short term. It was observed that efonidipine reduced SBP by 18.2 ± 12.2 mmHg and DBP by 10.7 ± 7.0 mmHg at the end of 28 days of treatment period. At visit 4, efonidipine was observed to be non-inferior to amlodipine in reducing the mean systolic as well as diastolic blood pressure (Table 2).

T- type Ca^{2+} channels are also located in SA node area. The blockade of T- type Ca^{2+} channels by efonidipine decreases the elevated heart rate due to prolongation of late phase-4 depolarization of the sinoatrial (SA) node action potential (25). In a clinical study, hypertensive patients treated with other CCBs except efonidipine were switched to efonidipine 40 mg for 4 weeks and it was observed that the R-R interval was significantly prolonged and the heart rate was reduced. This activity being unique to T-type Ca^{2+} channels blockers, the resultant decrease in heart rate is prominent with efonidipine as compared to conventional CCBs (10). The slow, constant recovery of SBP after the initial drop may also contribute to heart rate reduction (14). In the current clinical study, once daily efonidipine was found to be effective in the reduction of heart rate. At visit 4, the mean heart rate was reduced by 8.1 ± 8.3 bpm with efonidipine and was non-inferior to the mean reduction achieved with amlodipine (Table 4) which can be attributed to its distinctive mechanism of action.

Blockade of L-type Ca^{2+} channels alone, results in reflex tachycardia due to the accompanied vasodilation. However, in case of efonidipine, there is no reflex tachycardia due to the direct suppression of late phase-4 depolarization in the SA node, which is produced by the blockage of T-type channels (14). In the present study, in the efonidipine treated group no incidence of reflex tachycardia was reported during the entire study duration (Table 8b). Efonidipine was well tolerated by the patients and its safety was found to be comparable to amlodipine (Table 8a). The blockade of L- and T-type Ca^{2+} channels equalize the

hydrostatic pressure throughout the capillary bed by equal arteriolar and venular dilatation, thus reducing vasodilatory edema (26) and hence efonidipine is associated with a much lower risk of peripheral oedema (<0.1%) as compared to amlodipine (>10% to up to 46% based on various studies) (16) (27). Other adverse events associated with efonidipine (headache, flushing, dizziness, constipation) are also less as compared to conventional CCBs (20). In the present study, the most frequently observed adverse events with efonidipine and amlodipine treatment are mentioned in table 8b. The overall safety profile of efonidipine was similar to that of amlodipine, the long term effects of the two treatments needs to be studied in further clinical trials.

The undeviating and unfavorable consequences of hypertension on any vascular bed can be correlated with the extent of elevated blood pressure. If renal vascular injury develops, the autoregulatory responses are compromised and the damage is expected to amplify (28). The afferent arterioles of the glomerulus express both L- and T- type Ca^{2+} channels while the efferent arterioles express only T-type Ca^{2+} channels. Conventional dihydropyridine CCBs primarily block the L-type Ca^{2+} channels, and cause preferential reduction of the afferent arteriolar resistance (29) which increases the intraglomerular pressure (30). T-type CCBs like efonidipine tend to decrease the intraglomerular pressure, reduce pre as well as post-glomerular capillary resistance thus alleviating glomerular hypertension (13). This could wield a protective effect on renal injury progression. The renoprotective effects of efonidipine were not evaluated in the present study because of the shorter duration of treatment.

Contractions of microvasculature due to elevated hypertension have negative effect on renal perfusion and contribute to renal injury. T-type and L-/T- type Ca^{2+} channel blockers produce a significantly greater inhibition of contractions as compared to L-type Ca^{2+} channel blockers because of abundance of T-type Ca^{2+} channels in microvessels (31).

Constriction of afferent arterioles results in release of renin which ultimately leads to activation of angiotensin-II (32). Efonidipine prevents contraction of smooth muscles by inhibition of PKC-mediated signaling pathway and suppresses both angiotensin II- and K^{+} -induced aldosterone secretion and is considered superior to mineralocorticoid receptor (MR) antagonists as it does not cause hyperkalemia (19) (33). In a clinical trial, it was reported that efonidipine significantly reduced plasma aldosterone and proteinuria as compared to amlodipine in patients with chronic glomerulonephritis (29). Additionally, T-type Ca^{2+} channel activation stimulates release of renin. This observation supports the prospect that T-type Ca^{2+} channel blockade inhibits angiotensin II production and, therefore, efonidipine would be anticipated to contribute in part to the efferent arteriolar vasodilation and reduction in proteinuria levels by Renin-Angiotensin-Aldosterone system (RAAS) manipulation (34). Direct comparison of renal effects of T-type and L-type CCBs in non-diabetic patients with chronic kidney disease (CKD) revealed more beneficial effects of T-type CCBs than L-type CCBs on renal endpoints (35). Published literature has reported that lower

entrations of efonidipine significantly inhibited nuclear factor kappa B (NF- κ B) in human mesangium cells as compared to nifedipine and verapamil subsequently arresting the progress of renal injury via cytokines (36). Rho kinase activation which also participates in renal injury is inhibited by efonidipine enhancing its renoprotective effect and preventing renal vascular fibrosis (37). These finding lends support to the possibility that efonidipine exerts renoprotective action independent of systemic blood pressure.

In a phase III study, a treadmill exercise tolerance test demonstrated that efonidipine significantly inhibited increase in heart rate and prolonged the maximal exercise duration during the test, as compared to nifedipine by reducing sympathetic nervous activity and increasing parasympathetic activity. The study supports the claim that efonidipine improves myocardial oxygen consumption and tissue blood flow in the ischemic region (10). In another study conducted on patients with stable effort angina, efonidipine 40 mg given once daily for a week showed an improvement in cardiac hemodynamics during maximum

exercise; an improvement in ischemic changes was detected on ECG confirming efonidipine to have an anti-anginal action (38). Efonidipine has been proven to increase coronary blood flow and coronary sinus outflow without significantly affecting the myocardial oxygen demand. This effect of efonidipine along with its negative chronotropic action is best suited for patients of angina and hypertensives with concomitant coronary artery disease (CAD) (23). Studies have also demonstrated the role of T-type Ca^{2+} channels in pathophysiology of arrhythmia and their association with ventricular myocytes during cardiac anomalies. Efonidipine has high selectivity towards T-type Ca^{2+} channels and has been observed to express anti-arrhythmic action along with prevention of supraventricular tachycardia and atrial remodeling in atrial fibrillation. This feature can be exploited for hypertensive patients with CAD and at a risk of suffering from arrhythmias (39).

Apart from being a potent antihypertensive, the additional T-type Ca^{2+} channel inhibition, long term therapy with efonidipine has protective and reparative effect on the blood vessels (23). Unmanaged hypertension causes a reduction in arterial compliance and increase in their stiffness. Cardio-Ankle Vascular Index (CAVI) was used to measure arterial stiffness in a clinical trial involving hypertensive diabetic patients. Efonidipine was proven to be significantly better than amlodipine in lowering CAVI (40) (41). Efonidipine has been demonstrated in *in vitro* studies to have antiatherogenic effect by inhibiting cholesterol esterification and degradation of β - very low density lipoprotein (β -VLDL) in the cells (41). Efonidipine has also been observed to improve basilar artery flow and reduce the risk of ischemic strokes by preferentially dilating the basilar artery. It may also aid in enhancement of cognitive functions as efonidipine improves local cerebral blood flow (41).

Oxidative stress induced by hypertension via decreasing nitric oxide (NO) bioavailability leads to vascular endothelial injury and dysfunction. Efonidipine increases NO bioavailability and is also known to improve endothelial function by preventing formation of oxidative metabolites: 8-hydroxy-2'-deoxy Guanosine (8-OH-dG) and Malondialdehyde - modified LDL thus confirming its antioxidant potential (42).

Efonidipine treatment decreases the levels of platelet activation markers (CD62P-, CD63-, PAC-1-, and annexin V) and micro particles (PDMPs and MDMPs), which are associated with platelet activation and monocyte activation. It also lowers some cell adhesion molecule levels. These findings suggest that efonidipine may inhibit the vascular damage in hypertensive patients with diabetes and subsequently lower the cardiovascular complications (43). These features make efonidipine a valuable candidate not only in management of hypertension and associated renal injury but also for associated morbidities.

Efonidipine via blockade of T-type Ca^{2+} channels can assist in restraining the hyperinsulinemia by lowering insulin resistance and consequently improve glycemic status in hypertensive patients with type 2 diabetes mellitus (T2DM) (44). In the present study, advantages of efonidipine in hypertensive patients with diabetes was not analyzed, however this property should be further explored to ascertain the same in Indian population.

Efonidipine was developed as a drug with slow onset and long duration of action and is approved in Japan as Landel and has been proven to reduce blood pressure and heart rate without affecting the cardiac output. Efonidipine causes reduction of heart rate and glomerular pressure thus exhibiting protective action on the heart and kidney, respectively (14). The results of the present clinical study indicate that efonidipine is non-inferior to amlodipine in reduction of SBD, DBP and heart rate, while known to being superior to conventional CCBs in renoprotective action and heart rate reduction.

4. CONCLUSION

Efonidipine was found to be comparable to amlodipine in management of hypertension and achieving the target BP <140/90 mm Hg and heart rate of <83bpm. The safety profile of efonidipine was concluded to be non-inferior to that of amlodipine. Further clinical studies on a larger patient pool and longer duration should be conducted to study the effects of efonidipine in terms of side effect profile and renoprotective activity.

CONSENT

Not Applicable

ETHICAL APPROVAL

"All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki."

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