Journal of Advances in Medicine and Medical Research

25(1): 1-12, 2018; Article no.JAMMR.38509
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

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

Bhupesh Dewan[1*] and Vaidehi Wani[1]

[1]Department of Medical Services, Zuventus Healthcare Ltd., Office No. 5119, Oberoi Garden Estate, Chandivali, Andheri (E), Mumbai-400 072, India.

Authors' contributions

This work was carried out in collaboration between both authors. Author BD designed the study, wrote the protocol and wrote the first draft of the manuscript. Author VW managed the literature searches, managed the analyses of the study and performed the statistical analysis. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2018/38509
Editor(s):
(1) Salomone Di Saverio, Emergency Surgery Unit, Department of General and Transplant Surgery, S. Orsola Malpighi University Hospital, Bologna, Italy.
Reviewers:
(1) Satoru Kuriyama, Jikei University School of Medicine, Japan.
(2) Germán Dominguez-Vías, University of Cádiz, Spain.
(3) Nina Filip, Grigore T. Popa University of Medicine and Pharmacy, Romania.
Complete Peer review History: http://www.sciencedomain.org/review-history/22727

Original Research Article

Received 29th October 2017
Accepted 6th January 2018
Published 13th January 2018

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

**Corresponding author: E-mail: Bhupesh.Dewan@zuventus.com;*

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 in 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 the Indian population. A total of 200 patients were randomized to receive either efonidipine 40 mg (n=95) or amlodipine 5 mg (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 the reduction of SBD, DBP, and heart rate and was found to be comparable to amlodipine in the 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 of 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 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 a 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 a 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 decreases 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. MATERIALS 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 a 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 A_1C) >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 5 mg given once daily orally in the 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 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 of the study was calculated using WINPEPI software at a level of significance of 5% (α=.05) and a power of 80% (β=.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 were analyzed descriptively and values were expressed as mean ± 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 that 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).

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 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).

Additionally, it was noted that by the end of the treatment phase, 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

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

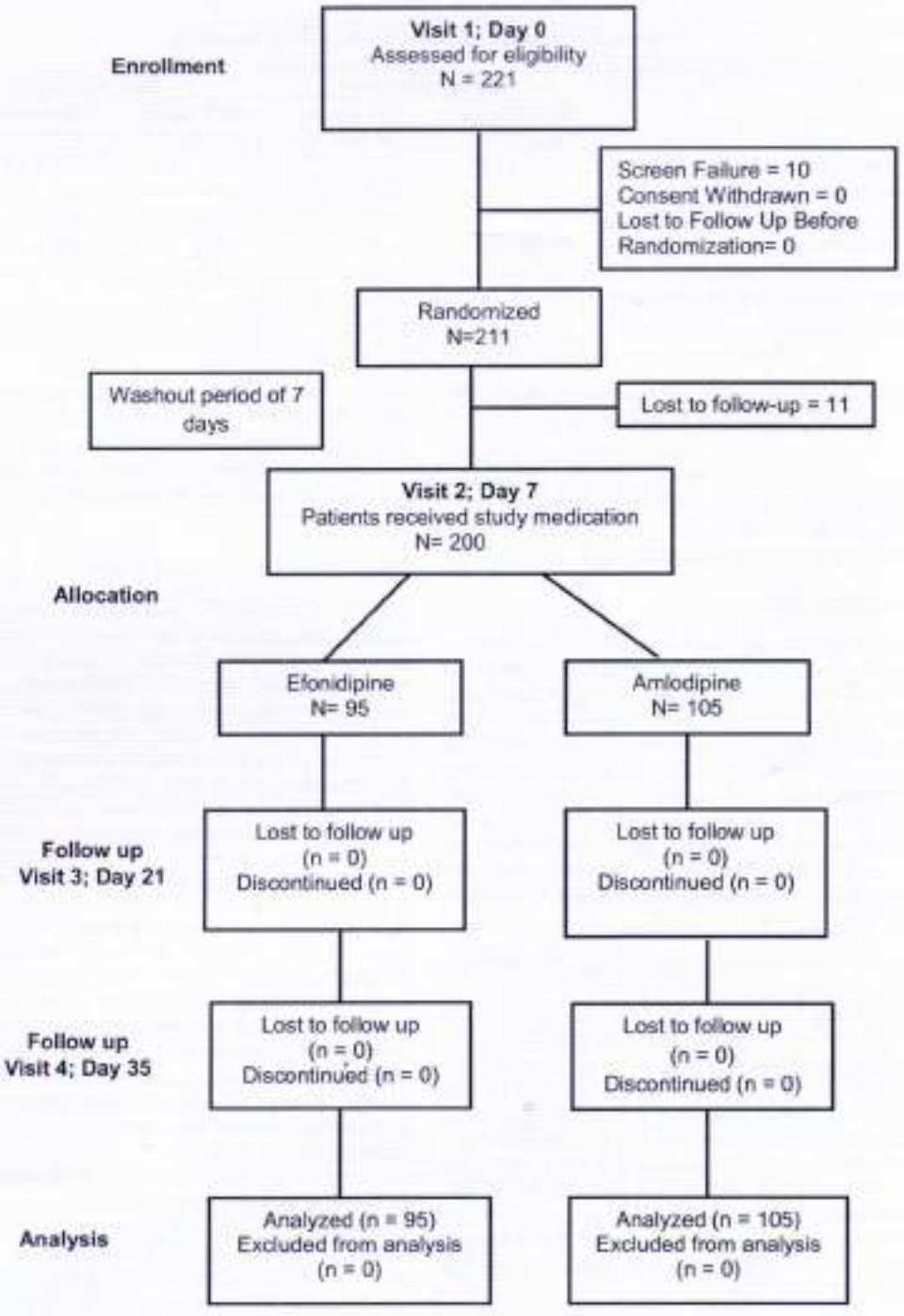

Fig. 1. Consort flow diagram

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 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

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).

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 phase. No significant difference (P =.35) was observed in the proportion of patients achieving the targeted heart rate between the two treatment groups (Table 5).

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).

3.3 Clinical Laboratory Tests

Clinical laboratory parameters such as 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.

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 the study. There was no statistically significant difference (P =.68) in the number of adverse events reported between the groups. The summary of 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.

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%

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 *P < .001 95% CI = -5.8 to -3.1 Mean Difference = 4.9 ± 8.8	82.3 ± 6.4 *P < .001 95% CI = -6.6 to -3.2 Mean Difference = 4.4 ± 6.7
Visit 4 (Day 35) bpm; Mean ± S.D.	80.6 ± 6.8 *P <.001 95% CI = -9.8 to -6.5 Mean Difference = 8.1 ± 8.3	79.9 ± 5.8 *P <.001 95% CI = -9.1 to -5.3 Mean Difference = 7.2 ± 9.9
Amlodipine vs. Efonidipine (Visit 4)	#P =.48; NS 95% CI = -1.6 to 3.5	

*Paired t-test; #Unpaired t-test

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.

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%)
P (Pearson's chi-squared test)	.35

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 [17].

CCBs, one of the front-runners of antihypertensive therapy are recommended by JNC 8 hypertension guideline as initial drugs of choice [18]. The influx of 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]. Therapy with conventional CCBs is accompanied by reflex tachycardia due to their vasodilatory effect [22].

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 [23,24,7]. 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 the 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).

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

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 10^3/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	0.2	0.7	2.0	-0.1	-1.4	22.2	-10.3	0.9	-4.6	-6.8
Mean Change from baseline	(-1.9 to 1.5)	(-2.6 to 1.2)	(-4.7 to 0.6)	(0.0 to 0.1)	(0.2 to 2.6)	(-284.9 to 240.4)	(-93.8 to 73.1)	(-2.6 to 0.7)	(-10.5 to 1.3)	(-2.2 to 15.7)
(95% CI), p	*P=.059	*P=.47	*P=.12	*P=.003	*P=.03	*P=.87	*P=.01	*P=.27	*P=.13	*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 10^3/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	0.1	1.2	0.0	0.0	0.1	242.4	-7.2	-1.9	-1.2	-1.5
Mean Change from baseline	(-1.6 to 1.4)	(-2.7 to 0.4)	(-1.6 to 1.6)	(-0.0 to 0.1)	(-1.1 to 0.9)	(-475.2 to -9.6)	(-96.8 to 82.5)	(-0.4 to 4.2)	(-2.7 to 5.1)	(-4.9 to 7.9)
(95% CI), p	*P=.21	*P=.14	*P=.97	*P=.08	*P=.84	*P=.04	*P=.11	*P=.10	*P=.53	*P=.65
Between the group comparison	0.1	-0.5	2.0	-0.1	-1.5	-220.2	-3.2	2.8	-3.4	-5.3
Efonidipine vs. Amlodipine	(-0.6 to 0.2)	(-2.8 to 3.0)	(-1.2 to 7.9)	(-0.0 to 0.1)	(-3.1 to 3.1)	(-404.1 to 557.5)	(-13.8 to 23.2)	(-2.9 to 2.9	(-2.3 to 13.6)	(-14.7 to 13.0)
Visit 4	#P=.39	#P=.95	#P=.14	#P=.17	#P=.99	#P=.75	#P=.62	#P=.97	#P=.17	#P=.90
Mean Change (95% CI), p										
*Paired t-test; #Unpaired t-test										

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

The blockade of T- type Ca^{2+} channels by efonidipine decrease 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 is 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.

Efonidipine was found to be 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, there was no incidence of oedema observed with efonidipine therapy. The most frequently observed adverse events with efonidipine and amlodipine treatment are mentioned in Table 8b.

The undeviating and unfavorable consequences of hypertension on any vascular bed can be correlated with the extent of elevated blood pressure. If a renal vascular injury develops, the autoregulatory responses are compromised and the damage is expected to amplify [28]. Efonidipine tend to decrease the intraglomerular pressure by reducing pre- as well as post-glomerular capillary resistance thus alleviating glomerular hypertension [13]. This could wield a protective effect on renal injury progression. Table number 7 shows the changes in Serum creatinine and Blood urea before and after the

treatment, but a longer period of observation is required to see significant changes in renal functioning. The renoprotective effects of efonidipine were not evaluated in the present study because of the shorter duration of treatment.

Efonidipine prevents contraction of smooth muscles by inhibition of PKC-mediated signaling pathway and suppresses both angiotensin II- and K^+-induced aldosterone secretion and does not cause hyperkalemia [19,29]. Efonidipine has also been reported to significantly reduce proteinuria as compared to amlodipine [30]. Published literature has also reported that lower concentrations of efonidipine significantly inhibited nuclear factor kappa B (NF-κB) in human mesangium cells as compared to nifedipine and verapamil subsequently arresting the progress of renal injury via cytokines [31]. Rho kinase activation which also participates in renal injury is inhibited by efonidipine enhancing its renoprotective effect and preventing renal vascular fibrosis [32]. These finding lends support to the possibility that efonidipine exerts renoprotective action independent of systemic blood pressure.

Efonidipine was found to inhibit increase in the heart rate and prolonged the maximal exercise duration during the treadmill test, as compared to nifedipine by reducing sympathetic nervous activity and increasing parasympathetic activity [10]. 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 [33,34]. 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 [34]. 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 the enhancement of cognitive functions as efonidipine improves local cerebral blood flow [34].

Efonidipine treatment decreases the levels of platelet activation markers (CD62P-, CD63-, PAC-1-, and annexin V) and microparticles (PDMPs and MDMPs), which are associated with platelet activation and monocyte activation [35]. These features make efonidipine a valuable candidate not only in the management of hypertension and associated renal injury but also for other related 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) [36].

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 be superior to conventional CCBs in renoprotective action and heart rate reduction.

4. CONCLUSION

Efonidipine was found to be comparable to amlodipine in the 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

It is 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.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. NICE. Hypertension in adults: Diagnosis and management. 2016;(August 2011).
2. Fujita T, Ando K, Nishimura H, Ideura T, Yasuda G, Isshiki M, et al. Antiproteinuric effect of the calcium channel blocker cilnidipine added to renin-angiotensin inhibition in hypertensive patients with chronic renal disease. Kidney Int. Elsevier Masson SAS. 2007;72(12):1543–9.
3. Wright JT, Bakris G, Greene T, Appel LJ, Cheek D, Douglas-baltimore JG, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease. 2002;288(19):2421–32.
4. Homma K, Hayashi K, Yamaguchi S, Fujishima S, Hori S, Itoh H. Renal microcirculation and calcium channel subtypes. Curr Hypertens Rev. 2013;9(3):182–6.
5. Bucci C, Mamdani MM, Juurlink DN, Tu J V. Dihydropyridine calcium channel blockers and cardiovascular outcomes in elderly patients: A population-based study. Can J Cardiol. 2008;24(8):629–32.
6. Perez-Reyes E. Molecular physiology of low-voltage-activated t-type calcium channels. Physiol Rev. 2003;83(1):117–61.
7. Shimizu M, Ogawa K, Sasaki H, Uehara Y, Otsuka Y, Okumura H, et al. Effects of efonidipine, an L- And T-Type dual calcium channel blocker, on heart rate and blood pressure in patients with mild to severe hypertension: An uncontrolled, open-label pilot study. Curr Ther Res - Clin Exp. 2003;64(9):707–14.
8. Tanaka H, Shigenobu K. Pathophysiological significance of T-type Ca2+ channels: T-type Ca2+ channels and drug development. J Pharmacol Sci. 2005;99:214–20.
9. Opie LH. Calcium channel antagonists part IV: Side effects and contraindications drug interactions and combinations. Cardiovasc Drugs Ther. 1989;3(4):480.
10. Harada K, Nomura M, Nishikado A, Uehara K, Nakaya Y, Ito S. Clinical efficacy of efonidipine hydrochloride, a T-type calcium channel inhibitor, on sympathetic activities. Circ J. 2003;67(2): 139–45.
11. Okayama S, Imagawa K, Naya N, Iwama H, Somekawa S, Kawata H, et al. Blocking T-type Ca2+ channels with efonidipine decreased plasma aldosterone concentration in healthy volunteers. Hypertens Res. 2006;29(7):493–7.
12. Masuda Y, Iwama T, Yamashita T, Sakai T, Hibi M, Tanaka S, Shigenobu K KY. Cardiac and vascular effects of NZ - 105, a novel dihydropyridine derivative, *in vitro*. Arch Int Pharmacodyn Ther. 1991;314:57–73.
13. Hayashi K, Homma K, Wakino S, Tokuyama H, Sugano N, Saruta T, et al. T-type Ca channel blockade as a determinant of kidney protection. Keio J Med. 2010;59(3):84–95.
14. Tanaka H, Shigenobu K. Efonidipine hydrochloride: A dual blocker of L- and T-type ca(2+) channels. Cardiovasc Drug Rev. 2002;20(1):81–92.
15. Chobanian Aram V, Bakris George L, Black Henry R, Cushman William C, Green Lee A, Izzo Joseph L Jr, Jones Daniel W, Materson Barry J, Oparil Suzanne, Wright Jackson TJ, Roccella Edward J, the NHBPEPCC. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 200AD;42:1206–52.
16. Galappatthy P, Wanigarayake YC, Sabeer MIM, Wijethunga TJ, Galappatthy GKS, Ekanayaka RA. Leg edema with (S)-amlodipine vs conventional amlodipine given in triple therapy for hypertension: A randomized double blind controlled clinical trial. BMC Cardiovasc Disord. BMC Cardiovascular Disorders. 2016;16(1):168.
17. Armstrong C. Practice guidelines JNC 8 guidelines for the management of hypertension AAFP's "Five key metrics for financial success." Am Fam Physician. 2014;90(7):503–4.
18. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS OE. Evidence-based guideline for the management of high blood pressure in adults: (JNC8). JAMA. 2014;311(5):507–20.
19. Hermsmeyer KMK. Protein kinase C mechanism enhances vascular muscle relaxation by the Ca2+ antagonist, Ro 40-5967. J Vasc Res. 1996;33(1):71–7.
20. Saruta T. Current status of calcium antagonists in Japan. Am J Cardiol. 1998;12(82(9B)):32R–34R.
21. Kubota K, Pearce GL IW. Vasodilation-

related adverse events in diltiazem and dihydropyridine calcium antagonists studied by prescription-event monitoring. Eur J Clin Pharmacol. 1995;48(1):1–7.

22. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. Lancet. 2008;372(9641): 2016–8.
23. Masuda Y, Tanaka S. Efonidipine hydrochloride: A new calcium antagonist. Cardiovasc Drug Rev. 1994;12(2):123–35.
24. Schwartz A. Molecular and cellular aspects of calcium channel antagonism. Am J Cardiol. 1992;70:6F–8F.
25. Masumiya H, Shijuku T, Tanaka H SK. Inhibition of myocardial L- and T-type Ca^{2+} currents by efonidipine: Possible mechanism for its chronotropic effect. Eur J Pharmacol. 1998;349(2–3):351–7.
26. Ge W, Ren J. Combined I-/I-type calcium channel blockers ready for prime time. Hypertension. 2009;53(4):592–4.
27. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults. JAMA. 2014;311(5):507.
28. Bidani AK, Griffin KA. Pathophysiology of hypertensive renal damage: Implications for therapy. Hypertension. 2004;44(5):595–601.
29. Keiichi Imagawa, Satoshi Okayama, Minoru Takaoka, Hiroyuki Kawata, Noriyuki Naya, Tamio Nakajima, Manabu Horii, Shiro Uemura and YS. Inhibitory effect of efonidipine on aldosterone synthesis. 2006;47(1):133–8.
30. Ishimitsu T, Kameda T, Akashiba A, Takahashi T, Ohta S, Yoshii M, et al. Efonidipine reduces proteinuria and plasma aldosterone in patients with chronic glomerulonephritis. Hypertens Res. 2007;30(7):621–6.
31. Hayashi M, Yamaji Y, Nakazato Y, Saruta T. The effects of calcium channel blockers on nuclear factor kappa B activation in the mesangium cells. Hypertens Res. 2000;23(5):521–5.
32. Sugano N, Wakino S, Kanda T, Tatematsu S, Homma K, Yoshioka K, et al. T-type calcium channel blockade as a therapeutic strategy against renal injury in rats with subtotal nephrectomy. Kidney Int. Elsevier Masson SAS. 2008;73(7):826–34.
33. Shirai K, Hiruta N, Song M, Kurosu T, Suzuki J, Tomaru T, et al. Cardio-ankle vascular index (CAVI) as a novel indicator of arterial stiffness: Theory, evidence and perspectives. J Atheroscler Thromb. 2011;18(11):924–38.
34. Sasaki H, Saiki A, Endo K, Ban N, Yamaguchi T, Kawana H, et al. Protective effects of efonidipine, a T- and L-type calcium channel blocker, on renal function and arterial stiffness in type 2 diabetic patients with hypertension and nephropathy. J Atheroscler Thromb. 2009;16(5):568–75.
35. Nomura S, Kanazawa S, Fukuhara S. Effects of efonidipine on platelet and monocyte activation markers in hypertensive patients with and without type 2 diabetes mellitus. J Hum Hypertens. 2002;16(8):539–47.
36. Li M. Role of T-type Ca2+ Channels in Basal insulin release BT - T-type calcium channels in basic and clinical science. In: Schaffer SW, Li M, editors. Vienna: Springer Vienna. 2015;137–50.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history/22727