Original Research Article

Antihypertensive efficacy and safety of the fixed-dose combination of Efonidipine and Chlorthalidone in Indian patients

ABSTRACT

Aim: This study aimed at evaluating the efficacy and safety of fixed dose combination (FDC) of Efonidipine and Chlorthalidone in a randomized, Phase III trial setting.

Study design: Multicentric, randomized, double blind, parallel, comparative, active-controlled Phase III.

Place and Duration of Study: Six geographically distributed sites across India were involved in this trial.

Methodology: Present study enrolled patients of Indian origin who were diagnosed with Stage I or Stage II hypertension as per JNC VII guideline. A total of 240 hypertensive patients were randomized (1:1) to receive either FDC of Efonidipine 40 mg + Chlorthalidone 12.5 mg tablet (E+C group) or FDC of Cilnidipine 10 mg + Chlorthalidone 12.5 mg tablet (C+C group) once daily for 90 days. Patients were evaluated for changes in their blood pressure (BP) from baseline to Day 30, 60 and 90. BP was recorded as the mean of 3 consecutive measurements taken in sitting position. Number of patients achieving target BP as per JNC VIII guideline was also evaluated. The safety and tolerability were assessed based on the incidences of adverse events (AEs) and serious adverse events (SAEs) reported.

Results: The mean (±SD) Systolic BP (SBP) and Diastolic BP (DBP) at baseline was 159.10±11.43/101.19±10.03 mm Hg in the E+C group. After 30 days of treatment with E+C group, the mean (±SD) reduction in SBP/DBP of 25.13±16.23/16.11±10.35 mmHg was observed whereas at Day 60 reduction of 32.51±19.73/17.91±11.06 mm Hg was seen from baseline. The primary endpoint focused on evaluating the mean BP reduction from baseline at Day 90. As compared to baseline, BP decreased from 159.10±11.43/101.19±10.03 mm Hg to 118.95±15.31/ 81.59±3.78 mm Hg with a mean reduction of 40.15/19.60 mm Hg at day 90 in the E+C group. The secondary endpoint of target BP <140/90 mmHg attainment as per JNC VIII guideline, was also achieved in 90.99% of the patients given the E+C group regimen. Furthermore, it was observed that, 94% of the Stage I and 88% of the Stage II hypertensive patients achieved the target BP goal. Overall, 2.54% of patients from the E+C group reported adverse events (AEs) which were mild in severity and resolved without any sequelae at the end of the study. No unexpected AEs were reported, and the E+C group regimen was well tolerated.

Conclusion: It was concluded that FDC of Efonidipine 40 mg and Chlorthalidone 12.5 mg was efficacious in the management of hypertension in both Stage I and Stage II hypertensive patients. It was evident from the study results that clinically meaningful reductions in blood pressure was observed over a period of 90 days. The test drug was safe and well tolerated by the patients after being administered as a single tablet daily.

Keywords: Hypertension, fixed dose combination, Efonidipine, Chlorthalidone, blood pressure

1. INTRODUCTION

Cardiovascular disease (CVD) remains the cause of morbidity and mortality for both men and women worldwide. Hypertension, a leading cause of CVD, is defined as having a blood pressure (BP) of at least 130/80 mm Hg or taking antihypertensive therapy. Yet, in a recent study, only 77% of individuals were aware that they had hypertension, and only 44% of those with hypertension had their BP controlled to <140/90 mm Hg in 2018. [1] Although it is straightforward to diagnose hypertension and relatively easy to treat the condition, the study revealed significant gaps in diagnosis and treatment. About 580 million people with hypertension (41% of women and 51% of men) were unaware of their condition because they were never diagnosed. The study also indicated that more than half of people (53% of women and 62% of men) with hypertension, or a total 720 million people, were not receiving the treatment that they need. Blood pressure was controlled, which means medicines were effective in bringing blood pressure to normal ranges, in fewer than 1 in 4 women and 1 in 5 men with hypertension. [2] Around 7.5 million deaths or 12.8% of the total of all annual deaths worldwide occur due to high blood pressure. It is predicted to be increased to 1.56 billion adults with hypertension in 2025.[3]

Uncontrolled hypertension is an independent risk factor for CVD, stroke, kidney disease, and cognitive decline and significantly contributes to complications of pregnancy and mortality globally. [1] Improving the effective coverage of treatment for patients with hypertension has become an objective of many global, regional, and national initiatives, and programmes.[4] Effective pharmacologic management is central to hypertension control. However, with the increasing number and diversity of pharmacologic agents available, spanning several key and complementary drug classes, treatment options are now complex and need to be simplified. One potential untapped means of simplifying the pharmacologic management of hypertension is through the use of fixed-dose combination (FDC) agents, in which two or more drugs are present in a single pill or capsule. This approach, which is not novel, has been widely underutilized. Increasing the use of FDC therapy could significantly and rapidly improve hypertension control rates and clinical outcomes in hypertension.[5] Initial combination therapy is associated with a 34% risk reduction in cardiovascular events as compared to monotherapy, and more rapid achievement of target blood pressure.[6]

While early and aggressive treatment with multiple drugs translates into a greater pill burden and alters the patient compliance to treatment thus making it difficult to achieve maximum clinical benefit. Poor medication adherence is associated with inadequate BP control. FDCs are an attractive option, as they have improved antihypertensive efficacy due to the dual mechanistic actions of the components, which target different effector mechanisms; each may counteract the counter-regulatory system activity triggered by the other. In addition, each drug of the fixed dose combination may negate adverse effects of the other medication. FDCs are also. Above all, FDCs improve medication compliance, which can translate into better cardiovascular outcomes and are a valuable tool to improve adherence in patients with hypertension.[7,8]

Diuretic/calcium channel blocker (CCB) combinations, which are supported by significant long-term evidence, are put forth as a preferred combination in the main guidelines, but are still underused by physicians who do not yet have easy access to such treatments. These combinations are listed as a preferred combination in the new European guidelines because they have been the focus of specific clinical trials. The newly published American Heart Association (AHA)/American College of Cardiology (ACC)/Centers for Disease Control (CDC) algorithm for high blood pressure management also recommends a thiazide diuretic/CCB combination for patients not controlled with a monotherapy and as a first-line

therapy. As most hypertensive patients will not achieve control on monotherapy, combination treatment with a diuretic and a CCB may offer a worthwhile alternative.[9]

Efonidipine is an antihypertensive and antianginal drug that blocks both, L- and T-type Ca^{2+} channels. It differs chemically from most other DHP with Ca2+ channel blocking properties in having a phosphonate moiety in position 5 of the DHP ring which is important for the characteristic pharmacological profile of the drug.[10] Apart from this, additional T-type calcium channel inhibition is responsible for its negative chronotropic, renoprotective and cardioprotective effects.[11]

Chlorthalidone is a thiazide-like sulfonamide-derived diuretic generally used as a first-line agent for the treatment of hypertension. Chlorthalidone exerts its therapeutic action by antagonizing sodium-chloride symporter in the distal convoluted tubule of the nephron. It is similar to a thiazide diuretic in its mechanism of action, although it has a mildly altered chemical structure. Both thiazide and thiazide-like diuretics contain a sulfonamide group that also works to inhibit carbonic anhydrase and its antagonistic action at the distal convoluted tubule.[12]

Considering the benefits associated, a randomized, comparative Phase III clinical trial in Indian hypertensive patients was conducted to evaluate the efficacy and safety of FDC of Efonidipine and Chlorthalidone (E+C).

2. MATERIAL AND METHODS

2.1 Study Design and Setting

The present study was a multicentric, randomized, double blind, parallel, comparative Phase III clinical trial in hypertensive patients of Indian origin. The trial was conducted in six geographically distributed sites across India.

The study was conducted in accordance with New Drugs and Clinical Trials, Rules, 2019, Ethical Guidelines for Biomedical Research on Human Participants, Indian Council of Medical Research (ICMR) 2017, International Council for Harmonization Guidelines (ICH) E6 (R2) for Good Clinical Practice, Declaration of Helsinki (World Medical Association [WMA]) and Ethical principles for medical research involving human subjects (Brazil, October 2013).

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. The trial was registered with the Clinical Trial Registry of India (Reg. No.: CTRI/2020/08/027364).

2.2 Study Subjects

The subjects were evaluated based on the inclusion and exclusion criteria. They underwent a screening procedure to determine their eligibility to participate in the trial. A total of 240 adult patients of Asian Indian Origin diagnosed with Stage I or Stage II hypertension were enrolled. The eligibility criteria for the patients to be enrolled in the study included the following: Patients aged ≥18 years. Patients with Stage I hypertension (SBP/DBP: 140-159/90-99 mmHg) or Stage II hypertension (SBP/DBP: ≥160/100 mmHg) as per JNC VII hypertension guidelines were included in the study and Patients who were able to switch all prior antihypertensive medications safely to study medication. All patients provided written informed consent to participate in the study. Patients were excluded from this study if they

had a history of hypersensitivity to dihydropyridine calcium channel blockers or diuretics, severe, malignant or secondary hypertension, cerebrovascular disease, second or third-degree atrioventricular block, chronic arrhythmia, sick sinus syndrome or sinus bradycardia, pregnant or breast-feeding females. The disposition of subjects is shown in Figure 1.

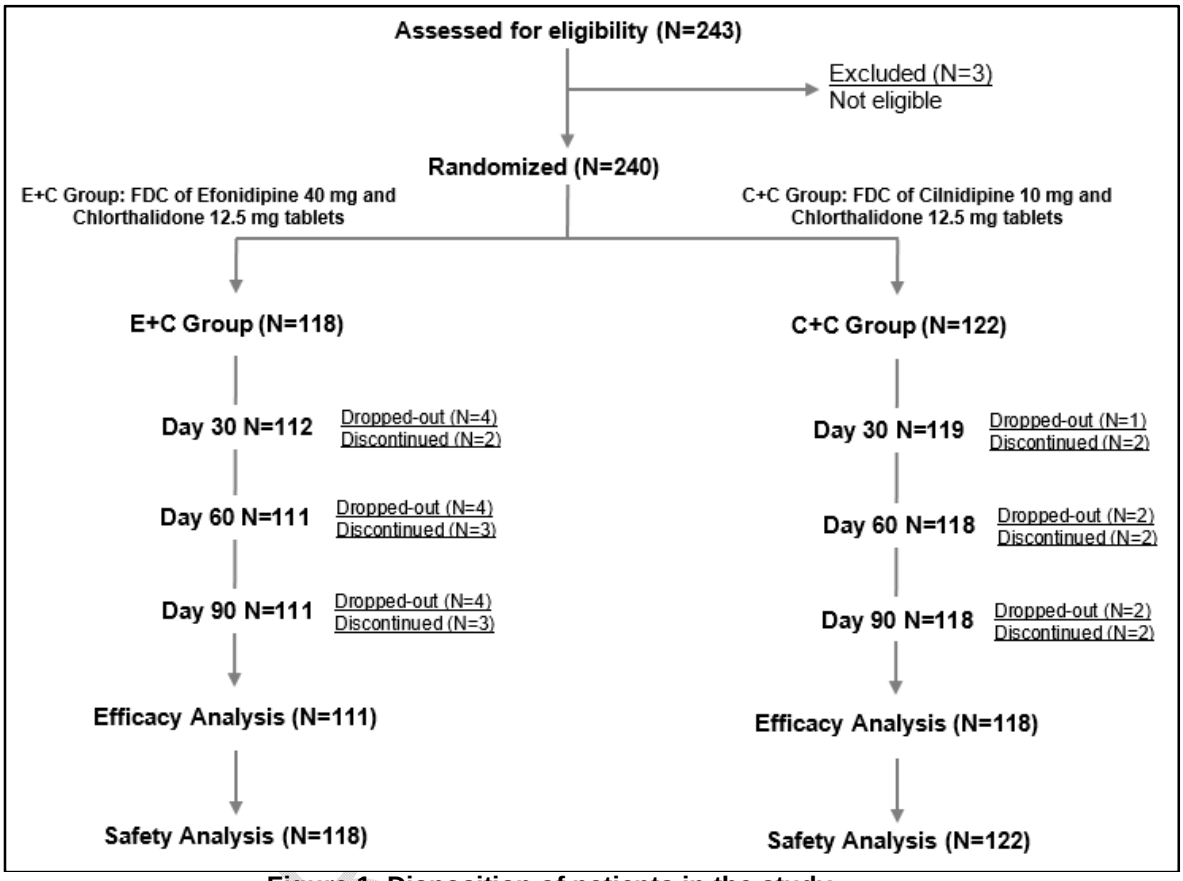

Figure 1: Disposition of patients in the study

2.3 Interventions

Eligible patients were randomized (1:1) to E+C or C+C group. The patients assigned to the E+C group received FDC of Efonidipine 40 mg and Chlorthalidone 12.5 mg tablets and the C+C group received FDC of Cilnidipine 10 mg and Chlorthalidone 12.5 mg tablets. The medication was administered once daily for 90 days. For treatment compliance, all enrolled patients were provided a patient diary that had information about the schedule of medicine administration for 90 days. At each follow-up visit, the patient was assessed for treatment compliance through the questionnaire and patient diary.

2.4 Outcome measures

The treatment duration was 90 with four visits including screening followed by Day 30, 60 and 90. At each visit, sitting SBP, DBP and heart rate were recorded. For each patient, blood pressure and heart rate were measured after patients were seated for at least 15 minutes. Three consecutive recordings were taken, each separated by at least 2 minutes. The mean of the 3 blood pressure values was calculated and recorded.

The primary endpoint of the present study was the change in SBP and DBP from the baseline to Day 90. The secondary endpoints of the study were the change in SBP and DBP from the baseline to Day 30 and 60, the number of patients achieving target blood pressure (defined as percentage of patients with sitting SBP <140 mmHg and DBP <90 mmHg) and the safety of the study treatments throughout the study period.

2.5 Data analysis

Descriptive statistics were used to summarize baseline characteristics in mean ± standard deviation (SD) for continuous variables whereas frequency counts and percentages were established for categorical variables. Paired t-test was used to evaluate the mean change in blood pressure at Day 90 from baseline for comparison within the individual treatment group. Mean change in blood pressure at the end of the study from baseline was assessed using an unpaired t-test and 95% Confidence Intervals (CIs) for the true proportion were calculated for comparison between the two treatment groups. Safety was summarized descriptively, and adverse events were assessed as the frequency and proportion of patients reporting the event.

3. RESULTS

3.1 Study population

A total of 240 eligible patients were enrolled and randomized to receive either E+C or C+C group regimen in a 1:1 ratio. The mean age of the population was 48.19 (range 19-70) years. A total of 33% of patients were diagnosed with Stage I hypertension and 67% with Stage II hypertension at the time of enrolment. Criteria for categorizing these patients was predefined and as per JNC VII hypertension guidelines. At baseline, patients from both the treatment groups had similar SBP and DBP. Overall, demographic and baseline characteristics were comparable between the treatment groups. Table 1 represents the demographic and baseline characteristics of patients enrolled in the study.

Table 1: Patient demographic data and baseline characteristics

Baseline Characteristics		E+C (Mean ± SD)	C+C (Mean ± SD)	P value*
N		118	122	-
Age, years		47.10 ± 12.60 (19-70)	49.24 ± 11.03 (23-70)	0.1633
Height, cm		161.38 ± 7.56	159.53 ± 8.05	0.0682
Weight, Kg		63.24 ± 8.51	62.32 ± 8.52	0.4061
Body mass index, Kg/m2		24.33 ± 3.21	24.56 ± 3.50	0.5906
Pulse Rate, beats/min		78.78 ± 8.81	79.14 ± 9.16	0.7568
Respiratory Rate, bpm		18.38 ± 1.63	18.52 ± 1.82	0.5220
Blood Pressure				
Stage I	**SBP, mmHg**	147.01 ± 4.32 (140-157.67)	148.30 ± 4.48 (140.67-158)	0.2000
	DBP, mmHg	94.09 ± 3.33 (80-98.67)	93.80 ± 3.14 (84-98)	0.7008

Stage II	**SBP, mmHg**	167.00 ± 9.19 (130.67-191.67)	167.29 ± 8.71 (140-195)	0.8397
	DBP, mmHg	105.00 ± 10.08 (82.33-120)	103.80 ± 10.44 (81.67-124-67)	0.4610
All patients	**SBP, mmHg**	160.40 ± 12.31 (130.67-191.67)	161.22 ± 11.70 (140-195)	0.5960
	DBP, mmHg	101.39 ± 9.90 (80-120)	100.61 ± 9.95 (81.67-124.67)	0.5413

**Unpaired t-test*

3.2 Primary Endpoint

3.2.1 Reduction in Blood Pressure at Day 90

After 90 days of E+C treatment, SBP reduced from 159.10 ± 11.43 mmHg to 118.95 ± 15.31 mmHg ($P < .0001$) with a mean difference of 40.15 mmHg and the DBP reduced from 101.19 ± 10.03 mmHg to 81.59 ± 3.78 mmHg ($P < .0001$) with a mean difference of 19.60 mmHg (Table 2).

It was noted that by the end of the treatment phase there was no statistically significant difference in mean change SBP ($P = .62$) and DBP ($P = .36$) between the two groups.

Table 2: Reduction in Blood Pressure from baseline at Day 90 with E+C treatment

Blood Pressure	N	Baseline	Day 90	Mean difference	*P* Value*
SBP (mmHg)	111	159.10 ± 11.43	118.95 ± 15.31	40.15 ± 20.91	<.0001
DBP (mmHg)	111	101.19 ± 10.03	81.59 ± 3.78	19.60 ± 11.20	<.0001

**Paired t-test, Values are in mean ± Standard deviation*

The changes in the SBP and DBP were compared from baseline to Day 90 in Stage I and Stage II hypertensive patients. Under treatment with the E+C regimen, a distinct decrease in mean SBP and DBP was observed over the course of 90 days. Over the same period, SBP and DBP fell by 21.24 and 11.91 mm Hg in patients with Stage I hypertension, and by 50.39 and 23.76 mm Hg in patients with Stage II hypertension (Table 3). When two treatment groups in Stage I and Stage II hypertensive patients were compared, it was found that there was no statistically significant difference in mean change in SBP (Stage I P=.29; Stage II P=.69) and DBP (Stage I; P=.95, Stage II; P=.80).

Table 3: Reduction in Blood Pressure from baseline at Day 90 in Stage I and Stage II hypertensive patients with E+C treatment

Blood Pressure	Baseline	Day 90	Mean difference	*P* Value*
Stage I (N=39)				
SBP (mmHg)	147.01 ± 4.32	125.77 ± 6.06	21.24 ± 7.50	<.0001
DBP (mmHg)	94.09 ± 3.33	82.17 ± 4.98	11.91 ± 4.57	<.0001
Stage II (N=72)				
SBP (mmHg)	165.64 ± 8.28	115.25 ± 17.44	50.39 ± 18.56	<.0001
DBP (mmHg)	105.04 ± 10.36	81.28 ± 2.93	23.76 ± 11.54	<.0001

**Paired t-test, Values are in mean ± standard deviation*

The efficacy of study treatments was evaluated in terms of non-inferiority between two treatment groups. The margin of non-inferiority was set to 10mmHg. The difference in systolic blood pressure between the E+C and C+C was 0.37 (*P*=.89, 95%CI: -4.91 to 5.66) and the difference in diastolic blood pressure was -0.04 (*P*=.98; 95% CI: -2.93 to 2.86). The upper boundary of the 95% CI was below the margin of 10 mmHg, confirming the non-inferiority of the E+C to the C+C treatment.

3.3 Secondary Endpoints

3.3.1 Target Blood pressure

After 30 days of E+C treatment, 70% of patients had achieved the target BP of <140/90 mmHg, and almost 84% were controlled after 2 months of E+C treatment (Day 60). After 3 months of treatment, 91% of patients achieved target BP demonstrating uniform efficacy of the E+C regimen. Table 4 presents details of the number of patients achieving the target goal of <140/90 mmHg.

Table 4: Number of patients achieved target BP goal with E+C treatment

Study population	Day 30 N(%)	Day 60 N(%)	Day 90 N(%)
All trial population	78/112 (69.64)	93/111 (83.78)	101/111 (90.99)
Stage I Hypertension	29/39 (74.36)	36/39 (32.31)	37/39 (94.87)
Stage II Hypertension	49/73 (67.12)	57/72 (79.17)	64/72 (88.89)

3.3.2 Blood pressure reduction at Day 30

In the E+C group, the SBP reduced from 159.10 ± 11.43 mmHg to 134.15 ± 12.56 mmHg at Day 30 with the mean reduction of 25.13 and the DBP reduced from 101.19 ± 10.03 mmHg to 85.01 ± 4.22 mmHg at Day 30 with the mean reduction of 16.11 (Table 5). The reduction in the average blood pressure was found to be statistically significant (*P* ≤ .0001). When two treatment groups were compared, it was found that there was no statistically significant difference in mean change SBP (*P* =.80) and DBP (*P* =.99).

Table 5: Reduction in Blood Pressure from baseline to day 30 with E+C treatment

Blood Pressure	Baseline	Day 30	Mean difference	*P* Value*
Overall population (N=112)				
SBP (mmHg)	159.10 ± 11.43	134.15 ± 12.56	25.13 ± 16.23	<.0001
DBP (mmHg)	101.19 ± 10.03	85.01 ± 4.22	16.11 ± 10.35	<.0001
Stage I (N=39)				
SBP (mmHg)	147.01 ± 4.32	135.04 ± 5.93	11.97 ± 5.85	<.0001
DBP (mmHg)	94.09 ± 3.36	84.01 ± 4.11	10.08 ± 4.22	<.0001
Stage II (N=73)				
SBP (mmHg)	165.83 ± 8.38	133.68 ± 14.97	32.16 ± 15.62	<.0001

DBP (mmHg)	104.88 ± 10.37	85.55 ± 4.20	19.33 ± 11.21	<.0001

**Paired t-test, Values are in mean ± standard deviation*

3.3.2 Blood pressure reduction at Day 60

In the E+C group, the SBP reduced from 159.10 ± 11.43 mmHg to 126.59 ± 14.65 mmHg at Day 60 with the mean reduction of 32.51 and the DBP reduced from 101.19 ± 10.03 mmHg to 83.28 ± 3.64 mmHg at Day 60 with the mean reduction of 17.91 (Table 6). The reduction in the average blood pressure was found to be statistically significant ($P \leq .0001$). When two treatment groups were compared, it was found that there was no statistically significant difference in mean change SBP ($P = .81$) and DBP ($P = .89$) between the two groups.

Table 6: Reduction in Blood Pressure from baseline to day 60 with E+C treatment

Blood Pressure	Baseline	Day 60	Mean difference	*P* Value*
Overall population (N=111)				
SBP (mmHg)	159.10 ± 11.43	126.59 ± 14.65	32.51 ± 19.73	<.0001
DBP (mmHg)	101.19 ± 10.03	83.28 ± 3.64	17.91 ± 11.06	<.0001
Stage I (N=39)				
SBP (mmHg)	147.01 ± 4.32	131.85 ± 5.90	15.16 ± 6.62	<.0001
DBP (mmHg)	94.09 ± 3.33	83.67 ± 4.64	10.42 ± 4.58	<.0001
Stage II (N=72)				
SBP (mmHg)	165.64 ± 8.28	123.74 ± 17.04	41.90 ± 18.03	<.0001
DBP (mmHg)	105.04 ± 10.36	83.07 ± 2.99	21.96 ± 11.44	<.0001

**Paired t-test, Values are in mean ± standard deviation*

3.3.3 Change in Heart rate

The mean change in the heart rate from baseline was analyzed in the trial population. The mean heart rate reduced from 78.66 ± 8.29 bpm to 77.33 ± 6.13 bpm ($P = .058$) in patients treated with E+C intervention. Similar results were observed for the C+C treatment. No statistically significant difference was observed in the reduction of the heart rate (P = .97) when the two treatment groups were compared.

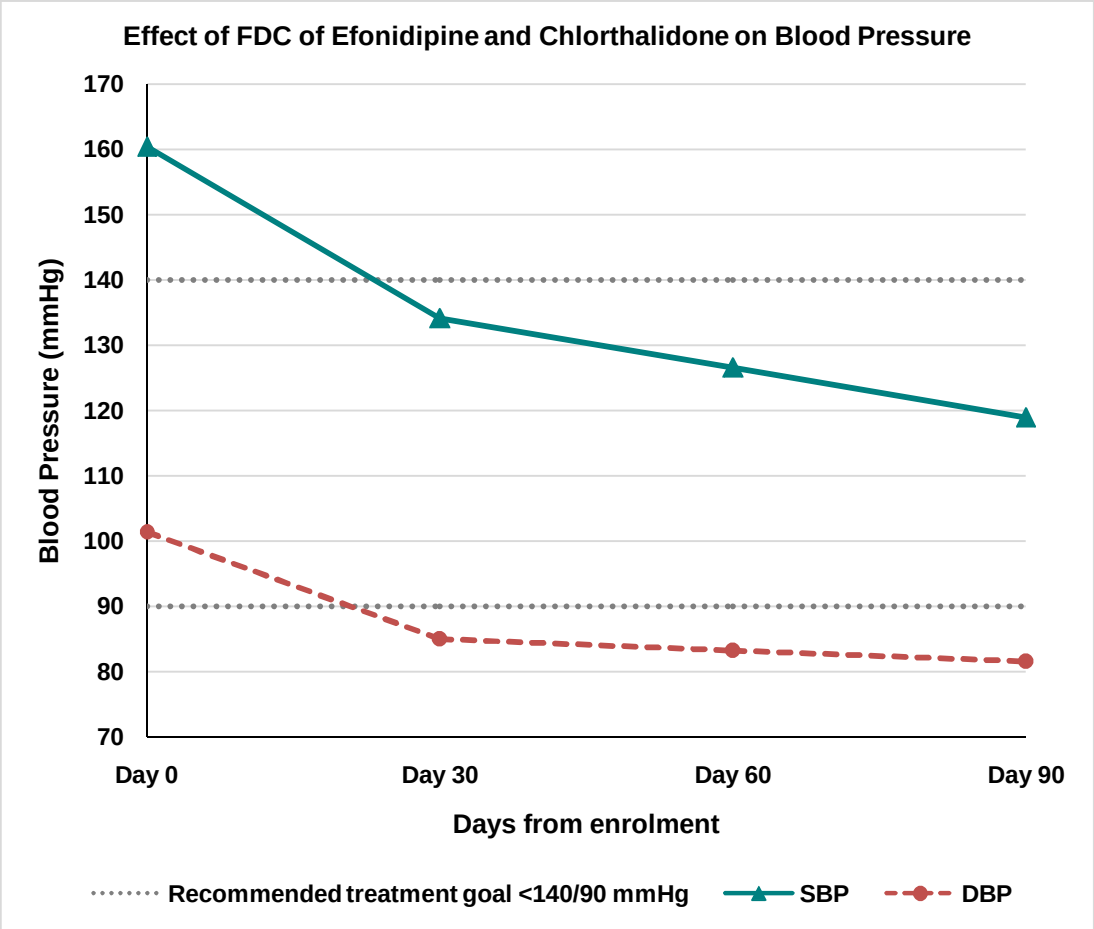

Figure 2: Reduction in Systolic and Diastolic Blood Pressure after E+C treatment

3.3.4 Analysis of Adverse events (AEs)

Safety was evaluated based on the incidences of AEs reported during the study. There were 06 AEs reported in 06 patients during the study period. In the E+C group, 3 AEs (low BP, urinary urgency, weakness) were reported in 3 patients whereas 3 AEs (fever, weakness, low BP) were reported in 3 patients in the C+C group. All adverse events were mild to moderate in severity. Three patients of the E+C group were discontinued from the study due to AEs reported. At the end of the study all AEs were resolved without any sequelae. A total of 2.54% patients experienced adverse events in the E+C group whereas 2.46% in C+C group. Both the investigational products were well tolerated by the patients on administration as a single pill for Day 90. No new or unexpected AEs/SAEs were reported with either of the study products in this study.

3.3.5 Clinical Laboratory evaluation

Clinical laboratory parameters, serum creatinine, blood urea nitrogen, total bilirubin, SGOT, SGPT were assessed before the start of the treatment and after completion of E+C treatment (day 90). Details of laboratory tests are shown in Table 7.

Table 7: Changes in laboratory parameters with E+C treatment

Laboratory parameters	At baseline	At day 90
Serum Creatinine (mg/dL)	0.90 ± 0.36	0.81 ± 0.15
eGFR (ml/min/1.73 m^2)	98.42 ± 16.35	98.07 ± 12.68
BUN (mg/dL)	14.52 ± 4.82	12.82 ± 3.80
Total Bilirubin (mg/dL)	0.71 ± 0.35	0.71 ± 0.22
SGOT (IU/L)	32.56 ± 8.15	33.79 ± 5.78
SGPT (IU/L)	31.42 ± 10.15	32.44 ± 7.68

Values are in mean ± standard deviation

3.3.5 Dosage compliance

The study drug compliance was assessed at each visit by tablet count or recording in the patient diary. Overall compliance was excellent with all patients identified as taking the prescribed study medication with dosage compliance being 94%. In this study, no patient reported less than 90% compliance. Thus, it can be concluded that simplified dosage regimens improve patient compliance especially when the dosage frequency is once daily.

4. DISCUSSION

Simplification of hypertension treatment by using Single Pill Combinations (SPCs) has received increasing support from most guidelines over the last few years. SPCs can simplify the task of adjusting and titrating the doses of their components and improve adherence. Moreover, patients on SPC experienced a lower 5-year rate of cardiovascular events than those on free combinations. Diuretics and CCBs are two major antihypertensive drug classes recommended for first line treatment.[13] CCBs and thiazide(-like) diuretics are widely used as monotherapy for the treatment of hypertension because they are effective in reducing cardiovascular morbidity and mortality and are well tolerated.[14]

CCBs represent a logical choice for antihypertensive therapy because of their remarkable efficacy in preventing stroke. However, when used in monotherapy, vasodilation produced by CCBs activates the RAAS and increases the incidence of peripheral edema, which can be counterbalanced by concomitant administration of a diuretic. Thiazide diuretics-based combinations have been widely prescribed for patients with hypertension.[15] The present clinical study comprising of 240 patients' documents efficacy and safety of the CCB/thiazide (-like) diuretic combination in reducing systolic and diastolic blood pressure. The reductions in SBP and DBP were statistically pronounced in patients receiving E+C group regimen.

Mortality outcome studies are important to allow decision making in the management of hypertension. However, tolerability, effectiveness, and cost of the medication and its delivery are other important criteria that influence the decision. Morgan *et.al*, noted that the results of his study together with outcome studies infer that in patients with essential hypertension it is appropriate to start therapy with a calcium channel-blocking drug or a diuretic at a low dose and if control is not achieved it is probably sensible to proceed to low dose dual therapy.[16] In the present study, under treatment with the E+C regimen, a remarkable decrease in mean SBP and DBP was observed over the course of 90 days. Over the same period, SBP and DBP fell by 21.24 and 11.91 mm Hg in patients with Stage I hypertension, and by 50.39 and 23.76 mm Hg in patients with Stage II hypertension. CCB diuretic combination is one of the

recommended options for managing hypertension with confirmed efficacy in terms of BP reduction and clinical outcomes, but remains underused in clinical practice.[13] Based on these findings, it can be suggested that that there is a place in everyday practice for this new treatment.

The combination of CCB/thiazide (-like) diuretics makes sense from a (patho)physiological point of view. Patients with isolated systolic hypertension are salt sensitive and display lower RAAS activity, both these factors favor the use of CCBs and diuretics. Furthermore, CCBs and diuretics have favorable effects on target organ damage and on cardiovascular hemodynamics, two important predictors of future cardiovascular risk that are particularly relevant in hypertensive patients.[14] From the study results, a distinctive decrease in the SBP and DBP after completion of the treatment phase was evident. It was illustrated from the results that the mean reduction in SBP was 40.15 mmHg and DBP was 19.60 mmHg at Day 90. A double-digit reduction in blood pressure was observed after only 30 days of administration. This indicates that CCB-based regimen can control BP levels. In addition, Costanzo *et. al*, in a meta-analysis observed that CCBs decreased the risk of fatal or nonfatal stroke. Several combination therapies with CCB and thiazide diuretic regimens are tested or widely used for the prevention of cardiovascular events in hypertension[17] suggesting beneficial role of E+C.

Hypertension is universally accepted as among the strongest prognostic markers of cerebrovascular disease and CVD and of premature death, with blood pressure values bearing a continuous linear relation with the incidence of cardiac and cerebrovascular events.[18] Clinical trials and observational studies indicate that initiating treatment with a 2-drug combination results in more rapid achievement of target BP compared with initial monotherapy.[19] Most national and international hypertension guidelines recommend a target BP of less than 140/90 mmHg.[20,21] After 30 days, 70% of patients had achieved the target BP and almost 84% were controlled after 2 months of E+C treatment (Day 60). At day 90, 91% of patients achieved target BP demonstrating uniform efficacy of the E+C regimen.

Incorporating an earlier and wider use of FDC drug therapy is a practical and effective strategy which has clear policy implications targeted to improve hypertension treatment and control worldwide. The overarching benefits to the patient, provider, and the health care system are numerous and apparent. The increasing role of FDC therapy in the treatment of hypertension, including in the initial treatment, is a new and key strategy to address this complex public health disease burden.[5]

5. CONCLUSION

In conclusion, the current study findings suggest that initiating fixed dose combination therapy resulted in clinically significant improvement in blood pressure control. Study results demonstrated that FDC of Efonidipine 40 mg + Chlorthalidone 12.5 mg was effective in the management of hypertension. The treatment was well tolerated by the patients after being administered as a single tablet daily for 90 days.

CONSENT

The authors declare that written informed consent was obtained from all the patients who participated in this study.

ETHICAL APPROVAL

The study protocol and related documents were approved by the Institutional Ethics Committee at each hospital study center. The 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 Declaration of Helsinki

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