Original Research Article

Efficacy and Safety of Fixed-Dose Combination of Efonidipine and Telmisartan in Stage II Hypertensive Patients

ABSTRACT

Aim: The aim of this study was to evaluate the anti-hypertensive efficacy of a fixed-dose combination (FDC) of Efonidipine 40 mg and Telmisartan 40 mg in Stage II hypertensive patients.

Study design: Multicentric, randomized, double-blind, parallel, comparative Phase III clinical trial.

Methodology: This clinical trial was conducted at six geographically distributed sites across India and enrolled 240 stage II hypertensive patients. They were randomized into two groups in a ratio of 1:1 to receive E+T (FDC of Efonidipine 40 mg + Telmisartan 40mg) or C+T (FDC of Cilnidipine 10 mg + Telmisartan 40 mg) group intervention once daily for a period of 90 days. The study site staff, investigator and patients were blinded to the treatment allocation. The primary endpoint of the study evaluated the mean reduction in sitting systolic BP (SBP) and diastolic BP (DBP) from baseline to day 90 whereas the secondary endpoints assessed were mean reduction in BP from baseline to day 30 & 60, patients achieving target BP (<140/90 mmHg) and the safety and tolerability of the investigational products based on the incidences of adverse events (AEs) reported.

Results: A total of 118 subjects were randomized to the E+T group wherein the mean (±SD) SBP and DBP at baseline was 167.25 ± 4.68/107.26 ± 5.19 mmHg. After 30 days of treatment with the E+T group, the mean reduction in SBP/DBP of 29.37/18.06 mmHg was observed whereas at Day 60 reduction of 38.55/22.69 mmHg was seen from the baseline. At Day 90, SBP/DBP decreased to 119.41±14.99/81.67±4.29 mmHg with a mean reduction of 47.94/25.89 mmHg in the E+T group. A total of 92% of patients who had been assigned to E+T treatment achieved their target BP goal. Only one patient reported an adverse event with E+T treatment. No unexpected AEs were reported in the E+T group suggesting its good safety and tolerability. Overall, the E+T treatment was effective, safe and well-tolerated by the patients for 90 days.

Conclusion: It was concluded that the FDC of Efonidipine 40 mg and Telmisartan 40 mg was efficacious in the management of Stage II hypertension. The study results illustrated a clinically meaningful reduction in blood pressure over a period of 90 days and achieving the target blood pressure.

Keywords: *Stage II hypertension, Fixed-dose combination, Efonidipine, Telmisartan*

1. INTRODUCTION

Cardiovascular disease is the leading cause of death in India (27%) as well as across the globe (31%) [1], and high blood pressure (BP) is a risk factor for cardiovascular disease and renal events [2]. Untreated or uncontrolled hypertension is the single largest contributor to the development of cardiovascular disease causing stroke, myocardial infarction, atrial fibrillation, heart failure, ischemic heart disease and chronic kidney disease [3].

High blood pressure affects more than 1 billion people worldwide, and that number is increasing due to rapid environmental and lifestyle changes. The prevalence of hypertension globally in adults aged 30-79 years is 32% in women and 34% in men and it has doubled since 1990 [4]. In India, a 15% prevalence was reported for hypertension (in 1990) and subsequently increased to 29.8% (in 2013) which is sustained over a period of time [5,6,7,8].

The highest risk for cardiovascular events is often found in patients with stage 2 hypertension, defined as blood pressure ≥160/100 mmHg [9]. Controlling hypertension is now recognized as the more important factor for cardiovascular and renal event risk reduction. The primary reason for inadequate BP control is the use of less-than-optimal treatment regimens. Blood pressure management and antihypertensive medications can effectively reduce an elevated BP and the risk of cardiovascular disease. Hypertension is always due to a variety of pathogenetic factors and multiregulated variables [10]. Thus, a strategy with monotherapy treatment makes it very difficult to normalize pressure by interfering through a single mechanism. In addition, monotherapy directed to any one of the components evokes compensatory responses and reduces the magnitude of BP control [11].

Combining two different classes of antihypertensive drugs reduces the BP five times more than doubling the dose of a single drug. In fact, 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 [12]. Randomized clinical trials and meta-analyses demonstrated a significant reduction in blood pressure and greater protection to a target organ with combination therapy than increasing the dose of monotherapy [13]. A systematic review of 14 randomized controlled trials (5120 participants) indicates a 27% (95%CI: 15-41%) improvement in blood pressure control with fixed-dose combinations of two drugs compared with monotherapy [14]. The Joint National Committee 7 (JNC7) guideline recommends treatment with combination therapy as initial therapy for achieving BP goals [15].

Fixed-dose combinations offer additional advantages, such as improvement in adherence to treatment, easier indication and cost-effectiveness than individual drugs [13]. A meta-analysis demonstrated that the use of FDCs was associated with significantly better compliance (n=17999, odds ratio: 1.21; 95% CI: 1.03 to 1.43; p=0.02) than its corresponding free-drug combinations. The odds ratio for adverse effects for use of FDC compared with the free-drug combination was 0.80 (95% CI: 0.58 to 1.11; p=0.19) [16].

The combination of drugs acts on different physiological systems and with complementary mechanisms of action provides benefits beyond BP lowering, such as improving tolerability, and thus higher rates of adherence to the prescribed medications as compared with increasing the dose of a single agent [17]. Both the eighth report of the Joint National Committee (JNC8) [18] and the 2018 guidelines of the European Society of Hypertension and the European Society of Cardiology (ESH/ESC) for the management of hypertension [19] recommend the use of combinations of antihypertensive agents preferably renin-angiotensin-system (RAS) blockers with calcium channel blocker (CCB) as initial therapy.

The test product used in this trial is a fixed-dose combination of Efonidipine (dihydropyridine dual CCB) and Telmisartan (Angiotensin II receptor blocker). Efonidipine is an antihypertensive and antianginal CCB that blocks both, L- and T-type Ca^{2+} channels, and acts on the cardiovascular system (vasodilator) with potent negative chronotropic and cardio-protective activity [20,21]. Telmisartan is a selective angiotensin II receptor antagonist which acts at the angiotensin II type 1 (AT1) receptor to block the effects of angiotensin II, namely vasoconstriction and aldosterone secretion [22]. Combination therapy attempts to block counter-regulatory responses that are activated by the perturbation of the blood pressure regulatory mechanisms when a physiological system is blocked with single-drug therapy [23]. CCB stimulates the renin-angiotensin system to compensate for the reduced pressure in the glomerular afferent arterioles and loss of sodium, whilst the Telmisartan inhibits the renin-angiotensin system at the AT1 receptor interfering the vasoconstriction [24,25].

Considering the prevalence of hypertension, poor control of hypertension with monotherapy, and the benefits of the E+T combination, the study was conducted to evaluate its efficacy and safety in Indian hypertensive patients.

2. MATERIAL AND METHODS

2.1 Design and Setting

The study was a multicentre, randomized, double-blind, active-controlled phase III clinical trial in Indian stage II hypertension patients. 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 centres. The trial was registered with the Clinical Trial Registry of India (Reg. No.: CTRI/2020/12/029739).

2.2 Participants

The participants 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 (≥18 years) patients of Asian Indian Origin diagnosed with Stage II hypertension (SBP/DBP: ≥160/100 mmHg) were enrolled. Patients were excluded from this study if they had hypersensitivity to CCBs or ARBs, a history of severe, malignant or secondary hypertension, or patients with 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.

2.3 Interventions

Eligible patients were randomly assigned using block randomization in a ratio of 1:1 to the E+T or C+T group. The assigned treatment arm was not known to the site staff, investigator and patients. Allocation concealment was done through the dispensation of the IPs in sealed sequentially numbered opaque envelopes. The patients assigned to the E+T group received FDC of Efonidipine 40 mg and Telmisartan 40 mg tablet and the C+T group received FDC of Cilnidipine 10 mg and Telmisartan 40 mg tablet. The medication was administered once daily for 90 days at approximately the same time each day. 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 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 the 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 30,60 and 90 from baseline for comparison within the treatment group. The mean change in blood pressure at the end of the study from baseline was assessed using an unpaired t-test. The results were presented with a significance level of 0.05 and 95% confidence intervals. Safety was summarized descriptively, and adverse events (AEs) were assessed as the frequency and proportion of patients reporting the event.

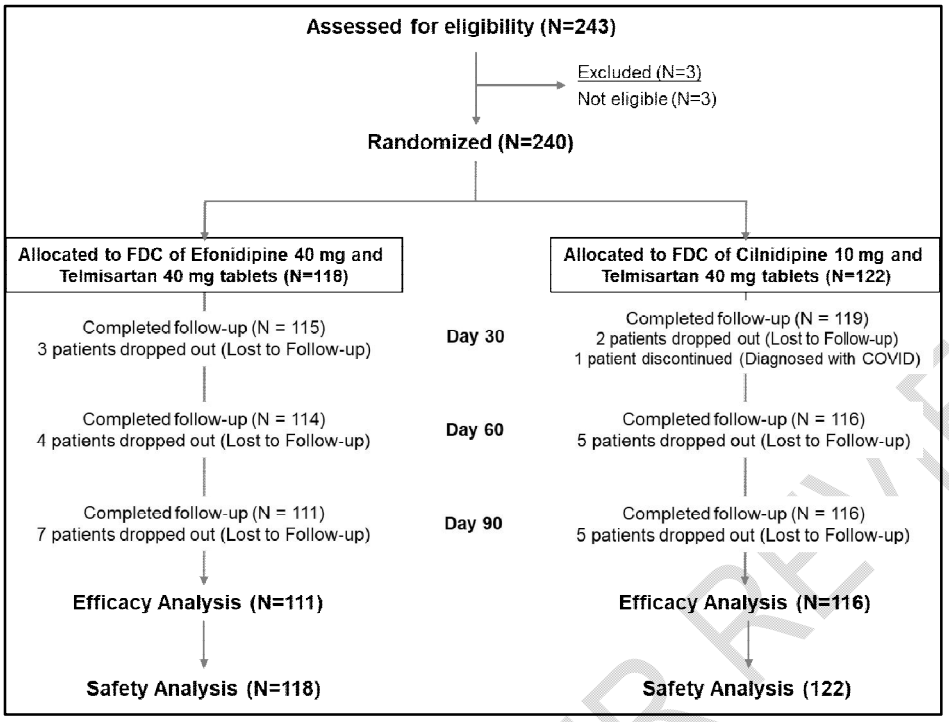

Figure 1: Disposition of patients in the study

3. RESULTS

3.1 Study Population

During the period of December 2020 - July 2021, 240 patients were enrolled and randomly assigned to E+T (N=118) and C+T (N=122) study treatments. The mean age of the population was 50.45 (range 22-70) years. At baseline, patients from both the treatment groups had similar SBP and DBP. All enrolled patients underwent ultrasonography during the screening to rule out renal artery stenosis. Overall, demographic and baseline characteristics were comparable between the treatment groups and presented in Table 1.

Table 1: Baseline characteristics and demographic data

Baseline Characteristics	E+T (Mean ± SD)	C+T (Mean ± SD)	p-value*
N	118	122	-
Age, years	51.03 ± 10.50	49.88 ± 10.48	0.40
Gender, n (%)			
Male	68 (57.63)	63 (51.64)	0.35#
Female	50 (42.37)	59 (48.36)	
Height, cm	162.09 ± 8.02	161.47 ± 8.39	0.56
Weight, kg	64.74 ± 9.27	64.41 ± 12.13	0.81

Body mass index, kg/m^2	24.69 ± 3.54	24.71 ± 4.42	0.97
Heart Rate, beats/min	77.59 ± 7.49	78.75 ± 6.55	0.20
Respiratory Rate, breaths/min	17.55 ± 2.10	17.84 ± 2.09	0.28
Blood Pressure			
SBP, mmHg	167.25 ± 4.68	167.14 ± 5.72	0.88
DBP, mmHg	107.26 ± 5.19	106.62 ± 5.40	0.35

**Unpaired t-test*
***Pearson chi^2 test*

3.2 Efficacy

3.2.1 Reduction in blood pressure at Day 90

At the end of the study, it was observed that in the E+T group, blood pressure reduced from 167.35 ± 4.67 mmHg to 119.41 ± 14.99 mmHg (p <0.0001) with a mean reduction of 47.94 mmHg in SBP and from 107.56 ± 5.15 mmHg to 81.67 ± 4.29 mmHg with a mean reduction of 25.89 mmHg in DBP. Both groups showed a significant reduction in BP as compared to the baseline (p<0.001). Between the two groups, it was noted that there was no statistically significant difference in the mean SBP (p = 0.80) and DBP reduction (p = 0.92) at day 90. (Tables 2 and 3)

The efficacy of study treatments was evaluated in terms of non-inferiority between the two treatment groups with the pre-specified margin of 10 mmHg. The difference in systolic blood pressure between the E+T and C+T was -0.48 (95%CI: -4.54 to 3.58) and -0.77 (95% CI: -2.60 to 1.06) for diastolic blood pressure. The upper boundary of the 95% CI was below the margin of difference between the two groups, confirming the non-inferiority of the E+T treatment to the C+T treatment.

Table 2: Reduction in systolic blood pressure from baseline to Day 90

	E+T (Mean ± SD)	**C+T (Mean ± SD)**	**Change in SBP Control vs. test**
Baseline	167.35 ± 4.67	167.37 ± 5.72	-
	**p = 0.97 (comparison between groups)		
Day 90	119.41 ± 14.99	119.90 ± 14.37	**p = 0.82 Mean Diff = -0.48 95% CI = -4.54, 3.58
	Mean Difference (95% CI) 47.94 (45.01, 50.88)	Mean Difference (95% CI) 47.46 (44.63, 50.29)	
	*p <0.0001 (Change from Baseline)	*p <0.0001 (Change from Baseline)	
	**p = 0.80 (comparison between groups)		

**Paired t-test; **Unpaired t-test*
E+T: FDC of Efonidipine 40 mg + Telmisartan 40 mg tablet
C+T: FDC of Cilnidipine 10 mg + Telmisartan 40 mg tablet

Table 3: Reduction in diastolic blood pressure from baseline to Day 90

	E+T (Mean ± SD)	C+T (Mean ± SD)	Change in DBP Control vs. test
Baseline	107.56 ± 5.15	106.84 ± 5.42	-
	**p = 0.31 (comparison between groups)		
Day 90	81.67 ± 4.29	81.73 ± 3.81	**p = 0.41 Mean Diff = -0.77 95% CI = -2.60, 1.06
	Mean Difference (95% CI) 25.89 (24.58, 27.20)	Mean Difference (95% CI) 25.11 (23.82, 26.41)	
	*p <0.0001 (Change from Baseline)	*p <0.0001 (Change from Baseline)	
	**p = 0.92 (comparison between groups)		

**Paired t-test; **Unpaired t-test*
E+T: FDC of Efonidipine 40 mg + Telmisartan 40 mg tablet
C+T: FDC of Cilnidipine 10 mg + Telmisartan 40 mg tablet

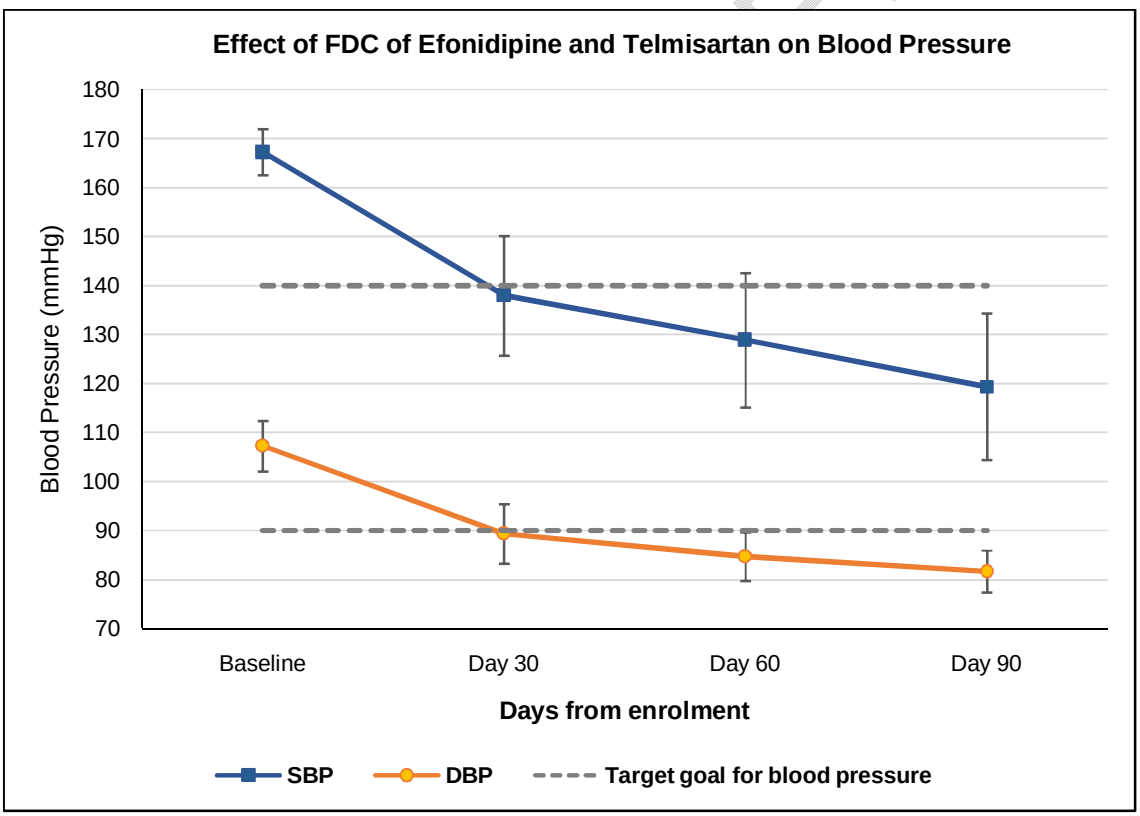

Figure 2: Reduction in Systolic and Diastolic Blood Pressure after E+T treatment

3.2.2 Target Blood pressure

The mean blood pressure of stage II hypertensive patients was below the target goal (<140/90 mmHg) within 30 days of treatment (Figure 2). After 30 days of E+T treatment, 63% of patients achieved the target BP and around 88% were controlled blood pressure after 60 days of E+T

treatment. At the end of the study, all patients who completed the study achieved target BP demonstrating uniform efficacy of the E+T regimen.

3.2.3 Reduction in blood pressure at Day 30

In the E+T group, the SBP reduced from 167.38 ± 4.66 mmHg to 138.01 ± 12.22 mmHg with a mean reduction of 29.37 mmHg and the DBP reduced from 107.40 ± 5.14 mmHg to 89.34 ± 6.11 mmHg with the mean reduction of 18.06 mmHg at Day 30 (Table 4). The reduction in the mean blood pressure was found to be statistically significant (p <0.0001) compared to the baseline. When the two treatment groups were compared, it was found that there was no statistically significant difference in mean SBP (p =0.40) and DBP (p = 0.61) reduction at Day 30.

Table 4. Reduction in blood pressure from baseline to day 30 with E+T treatment

Blood Pressure	Baseline	Day 30	Mean difference (95%CI)	*p* Value*
SBP (mmHg)	167.38 ± 4.66	138.01 ± 12.22	29.37 (26.97, 31.76)	<0.0001
DBP (mmHg)	107.40 ± 5.14	89.34 ± 6.11	18.06 (16.60, 19.52)	<0.0001

**Paired t-test*

3.2.4 Reduction in blood pressure at Day 60

In the E+T group, the SBP reduced from 167.43 ± 4.64 mmHg to 128.89 ± 13.71mmHg with a mean reduction of 38.55 mmHg and the DBP reduced from 107.43 ± 5.15mmHg to 84.75 ± 4.96 with the mean reduction of 22.69 mmHg at Day 60 (Table 5). The reduction in the mean blood pressure was found to be statistically significant (p < 0.0001). When the two treatment groups were compared, it was found that there was no statistically significant difference in mean SBP (p =0.80) and DBP (p =0.35) reduction at Day 60.

Table 5. Reduction in blood pressure from baseline to day 60 with E+T treatment

Blood Pressure	Baseline	Day 60	Mean difference (95%CI)	*p* Value*
SBP (mmHg)	167.43 ± 4.64	128.89 ± 13.71	38.55 (35.85, 41.24)	<0.0001
DBP (mmHg)	107.43 ± 5.15	84.75 ± 4.96	22.69 (21.29, 24.09)	<0.0001

**Paired t-test*

3.2.5 Change in Heart rate

The mean changes in heart rate from 77.11 ± 6.52 bpm to 77.09 ± 5.72 bpm (p=0.16) were observed in patients treated with E+T. Similar results were observed for the C+T treatment. No statistically significant difference was observed in the reduction of the heart rate (p = 0.33) when the two treatment groups were compared over a period of 3 months.

3.3 Safety Assessment

Safety assessment was based on the incidences of AEs reported during the study. There were 5 adverse events (AEs) reported in 2 patients, which included 1 patient in the E+T group who experienced headache, dizziness and vomiting. One patient of the C+T group experienced headache and nausea during the treatment period. At the end of the study, all AEs were resolved without any sequelae.

Clinical laboratory parameters were assessed before the start of the treatment and after the completion of E+T treatment (day 90). A significant increase in eGFR at day 90 was observed in the E+T group as compared to the baseline ($p<0.0001$). Details of laboratory tests are shown in Table 6.

Table 6. Changes in laboratory parameters with E+T treatment

Laboratory parameters	At baseline	At day 90
Serum Creatinine (mg/dL)	0.94 ± 0.21	0.96 ± 0.28
eGFR (ml/min/1.73m^2)	84.41 ± 16.05	93.36 ± 23.05
BUN (mg/dL)	13.78 ± 5.09	13.76 ± 6.41
Total Bilirubin (mg/dL)	0.72 ± 0.40	0.74 ± 0.35
Sodium (mEq/L)	139.41 ± 5.65	139.65 ± 3.96
Potassium (mEq/L)	4.18 ± 0.57	4.27 ± 0.62
SGOT (IU/L)	36.42 ± 15.32	34.45 ± 8.88
SGPT (IU/L)	36.83 ± 20.17	32.68 ± 10.38

Values are in mean ± standard deviation

4. Discussion

The use of multiple drug regimens is increasingly recognized as a tacit requirement for the management of hypertension, a necessity fueled in part by rising rates of metabolic syndrome. By targeting complementary pathways, combinations of antihypertensive drugs can be applied to provide effective blood pressure control while minimizing side effects and reducing exposure to high doses of individual medications [26]. The aim of combination therapy should always be to both improve BP control and reduce cardiovascular events. This is crucial to obtain additive BP-lowering effects without impacting tolerability. One typical combination (angiotensin receptor blocker and calcium antagonist) is the association of drugs blocking and stimulating the RAS [27]. A preferred use of these antihypertensive drug classes has been pursued by recent hypertension guidelines, in order to bridge the gap between the attained and expected BP control rates, to ensure adequate adherence and persistence to prescribed medications and to improve cardiovascular outcomes in treated patients with hypertension [18,19,28].

The major therapeutic mechanisms used for lowering high BP include AT1 receptor blockade and the regulation of intracellular Ca^{2+} concentration. AT1 receptor blockade is associated with the proliferation and migration of vascular smooth muscle cells - one of the main causes of atherosclerosis, and the intracellular Ca^{2+} concentration is important for vasodilation. Thus, the combination of a CCB with an ARB has been a rational strategy for the management of BP [29]. Several randomized clinical trials have also been conducted to evaluate the clinical benefits of ARB combined with CCB. In a meta-analysis that included seven RCTs with a study population ranging from 185 to 1,183 subjects, it was evident that adding an ARB to CCB after initial ineffective CCB monotherapy, significantly improved blood pressure control and the percentage of on-target hypertension treatment with significantly reduced incidence of adverse events compared with continued CCB monotherapy [30]. Similar kind of results were observed in the present clinical study involving 240 subjects documenting the efficacy and safety of one such CCB/ARB fixed-dose combination in reducing systolic and diastolic blood pressure in Stage II hypertensive patients. Efonidipine is a dihydropyridine calcium channel blocker (DHP-CCB) that inhibits both L-type and T-type calcium channels whereas Telmisartan is a biphenyl compound and benzimidazole derivative that acts as an AT1 receptor antagonist. Efonidipine has potent antihypertensive action and more favorable effects on renal function, oxidative stress and arterial stiffness than other CCBs. On the other hand, Telmisartan has a significant role in reducing cardiovascular morbidity and mortality in hypertensive patients [31,32].

The antihypertensive efficacy of the E+T group regimen was apparent from the study results. After 90 days of treatment, E+T intervention significantly reduced SBP and DBP in Stage II hypertensive patients wherein a mean reduction of 47.94 mmHg in SBP and 25.89 mmHg in DBP was observed. These findings are similar to the results observed for the FDC of Cilnidipine and Telmisartan combination in this trial and the results reported by Kondo et.al [33] for the FDC of Amlodipine and Telmisartan. It can be concluded from the study results that combination therapy with Efonidipine and Telmisartan led to efficient blood pressure reduction in stage II hypertensive patients.

In addition to BP-lowering efficacy, the tolerability of antihypertensive therapy is crucial as it affects patient compliance. Improved tolerability may potentially increase treatment adherence and thereby help attain the ultimate long-term goal of BP lowering, such as protecting patients from CV morbidity and mortality [34]. One of the most common dose-dependent adverse effects of CCBs is peripheral edema due to arteriolar dilatation. This effect is partially neutralized by RAAS inhibitor-induced venodilation. Additionally, RAAS inhibitors prevent tachycardia due to CCBs [35]. Efonidipine has lesser incidences of peripheral edema as compared to other dihydropyridine CCBs. In addition to this Efonidipine has fewer reported side effects as compared to other CCBs [20,36,37]. In this study, a total of three AEs (headache, dizziness, vomiting) were reported with Efonidipine and Telmisartan combination. Thus, less adverse events associated with the combination are reflected in this study.

Fixed-dose combination therapy comes as a possible solution to improve the treatment and control of high blood pressure. Moreover, the combination of two or more antihypertensive drugs in one tablet

acts with a synergistic mechanism reflecting better results in controlling BP levels [38]. Multi-drug combinations not only provide better BP control over the short term but also reduce physician inertia, and promote compliance and adherence. Thereby fixed-dose combination becomes convenient and cost-effective too. [39]

The study results represent the antihypertensive efficacy of FDC of Efonidipine and Telmisartan while mitigating the risks of treatment-related adverse events which represents a rational treatment strategy in the management of hypertension.

5. Conclusion

FDC of Efonidipine and Telmisartan (E+T) has the potential for the effective treatment of hypertension as a single convenient daily dose. In conclusion, fixed-dose combination therapy resulted in clinically significant improvement in the blood pressure control. The study results demonstrated that the FDC of Efonidipine 40 mg and Telmisartan 40 mg was effective and well-tolerated in the management of stage II hypertension.

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.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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