Original Research Article

EFFECT OF FIXED-DOSE COMBINATION OF EFONIDIPINE + S(-) METOPROLOL IN INDIAN HYPERTENSIVE PATIENTS

ABSTRACT

Aim: To evaluate the antihypertensive efficacy and safety of the fixed-dose combination (FDC) of Efonidipine and S (-) Metoprolol in adult patients with hypertension.

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

Methodology: This clinical trial was conducted at five geographically distributed sites across India and enrolled 240 hypertensive patients. They were randomized (1:1) to receive either FDC of Efonidipine 40 mg + S (-) Metoprolol 25 mg tablet (E+S(-)M group) or FDC of Cilnidipine 10 mg + Metoprolol 50 mg tablet (C+M group) once daily for 90 days. Patients were evaluated for changes in their blood pressure (BP) from baseline to Day 30, 60 and 90. The study site staff, investigator and patients were blinded to the treatment allocation. Blood pressure was recorded as the mean of 3 consecutive measurements taken in a sitting position. Patients achieving target BP (<140/90 mmHg) were evaluated and the safety and tolerability were assessed based on the incidences of adverse events (AEs).

Results: This study focused on evaluating the mean Systolic BP (SBP) and Diastolic BP (DBP) reduction from baseline to Day 30, 60 and 90. At baseline, patients had a mean (±SD) SBP and DBP of 154.60 (±11.33) mmHg and 98.68 (±8.18) mmHg respectively. After 30 days of the E+S(-)M treatment, the mean SBP/DBP was 136.06±10.55/ 86.68±5.51 mmHg (p<0.0001) and on Day 60 it was 129.48±10.51/ 84.17±5.51mmHg (P <0.0001), corresponding to mean reductions in SBP/DBP of 18.09/11.66 and 24.78/14.17 mmHg, respectively. There was a statistically significant (p <0.0001) reduction to 123.59 ± 15.21 mmHg in SBP and 82.38 ± 5.05 mmHg in DBP observed on Day 90 as compared to baseline. Post-treatment with E+S(-)M group, SBP/DBP reduction of 31.01/16.29 mmHg in hypertensive patients was observed. A total of 95% of the patients achieved a pre-defined target BP <140/90 mmHg on the administration of E+S(-)M. Furthermore, it was observed that 93% of Stage I and 96% of Stage II hypertensive patients achieved the target BP goal. A total of 5.78% of patients experienced adverse events (AEs) in the E+S(-)M group which was similar to that of C+M group. All AEs were mild in severity and resolved without any sequelae at the end of the study. No unexpected adverse events were reported, and the E+S(-)M dosage regimen was well tolerated by the patients. Both the treatment groups were non-inferior to each other

Conclusion: The study results demonstrated clinically meaningful reductions in blood pressure after administration of FDC of Efonidipine 40 mg + S(-) Metoprolol 25 mg over a period of 90 days. The treatment was efficacious, safe, and well tolerated in the study population.

Keywords: Hypertension, Fixed-dose combination, Efonidipine, S(-)Metoprolol, Blood pressure

1. INTRODUCTION

"Hypertension ranks among the most common chronic medical condition characterized by a persistent elevation in arterial pressure. It has been among the most studied topics of the previous century and has been one of the most significant comorbidities contributing to the development of stroke, myocardial infarction, heart failure, and renal failure. The definition and categories of hypertension have been evolving over years, but there is a consensus that persistent blood pressure (BP) readings of 140/90 mmHg or more should undergo treatment". [1]

"Globally, 59% of women and 49% of men were diagnosed with hypertension in 2019". [2] "The 2019–2020 National Family Health Survey (NFHS-5) of India reported a hypertension prevalence of 24% in men and 21.3% among women, an increase from 15% and 11% respectively from the previous round (2015–16)". [3] "The control rate of hypertension in India is dismal and only one-tenth of the rural and one-fifth the of urban Indian hypertensive population have their blood pressure (BP) under control". [4] "The high prevalence of hypertension and the current alarmingly poor control of blood pressure increases demands on healthcare resources. Prescribers are faced with a daunting array of antihypertensive agents with different mechanisms of action. Furthermore, many are ignoring the advantages of combination therapy, possibly because of a misconception that the patient may experience more side effects". [5]

Therapeutic treatment for hypertension is usually started as monotherapy, however, only 20%–30% of patients achieve recommended target BP goal. [6] "The strategy of doubling the dose of monotherapy to achieve the target BP has been repeatedly challenged. Such a strategy is unlikely to achieve the same BP-lowering effect in comparison with combination therapy. The combination of two different classes of antihypertensive drugs reduces the BP five times more than doubling the dose of a single drug". [7]

"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". [7] The 2018 ESC/ESH Hypertension Guideline recommended the use of fixed-dose combinations (FDCs) as an initiation of treatment for most patients with hypertension to improve the speed, efficiency, and predictability of BP control. [8]

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. In a meta-analysis that

included hypertensive patients, the use of a fixed-dose combination therapy improved adherence to treatment regimens by 24% compared with monotherapy or multiple-dose regimens. [9] Therefore, FDCs are the preferred strategy that not only provides better BP control but also reduces physician inertia (i.e. the delays in increasing dose or adding a second drug) and, promotes compliance and adherence. [10]

The integration of dihydropyridine (DHP) CCBs and beta-blocker is an ideal combination for the management of hypertension. Efonidipine, a dihydropyridine CCB and S(-)Metoprolol, a beta-blocker are frequently used as monotherapies to manage hypertension. [11,12] "These two antihypertensive agents have different complementary pharmacologic effects to reduce BP and exert an additive effect". [13]

"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 Ca^{2+} 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". [14] "Apart from this, additional T-type calcium channel inhibition is responsible for its negative chronotropic, renoprotective and cardioprotective effects". [15]

Metoprolol is a beta-1 selective adrenergic receptor-blocking agent. [16] It has enhanced therapeutic efficacy in existing FDCs as compared to other beta-blockers such as atenolol. [17] "Metoprolol is a racemic mixture of R(-) and S(-) Metoprolol. S(-)Metoprolol being a chirally pure enantiomer exhibits greater affinity and higher beta-1 receptor blocking activity than the R isomer with the S:R activity ratio being 33:1. It reduces the metabolic load by 50%. The beta-1 receptor affinity of S(-) Metoprolol is 500 times greater than that of R(-) Metoprolol".[18]

FDCs of antihypertensive medications, including FDC of Efonidipine and S(-)Metoprolol (E+S(-)M) have the potential to provide an effective hypertension therapy in a single convenient daily dose. Considering the prevalence of hypertension, poor control of hypertension in India and the benefits of the E+S(-)M 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 present study was a multicentric, randomized, double-blind, parallel-group, comparative Phase III clinical trial in hypertensive patients of Indian origin. The trial was conducted in five geographically distributed sites across India.

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 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. Patients were excluded from this study if they had a history of hypersensitivity to dihydropyridine calcium channel blockers or beta-blockers, 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.

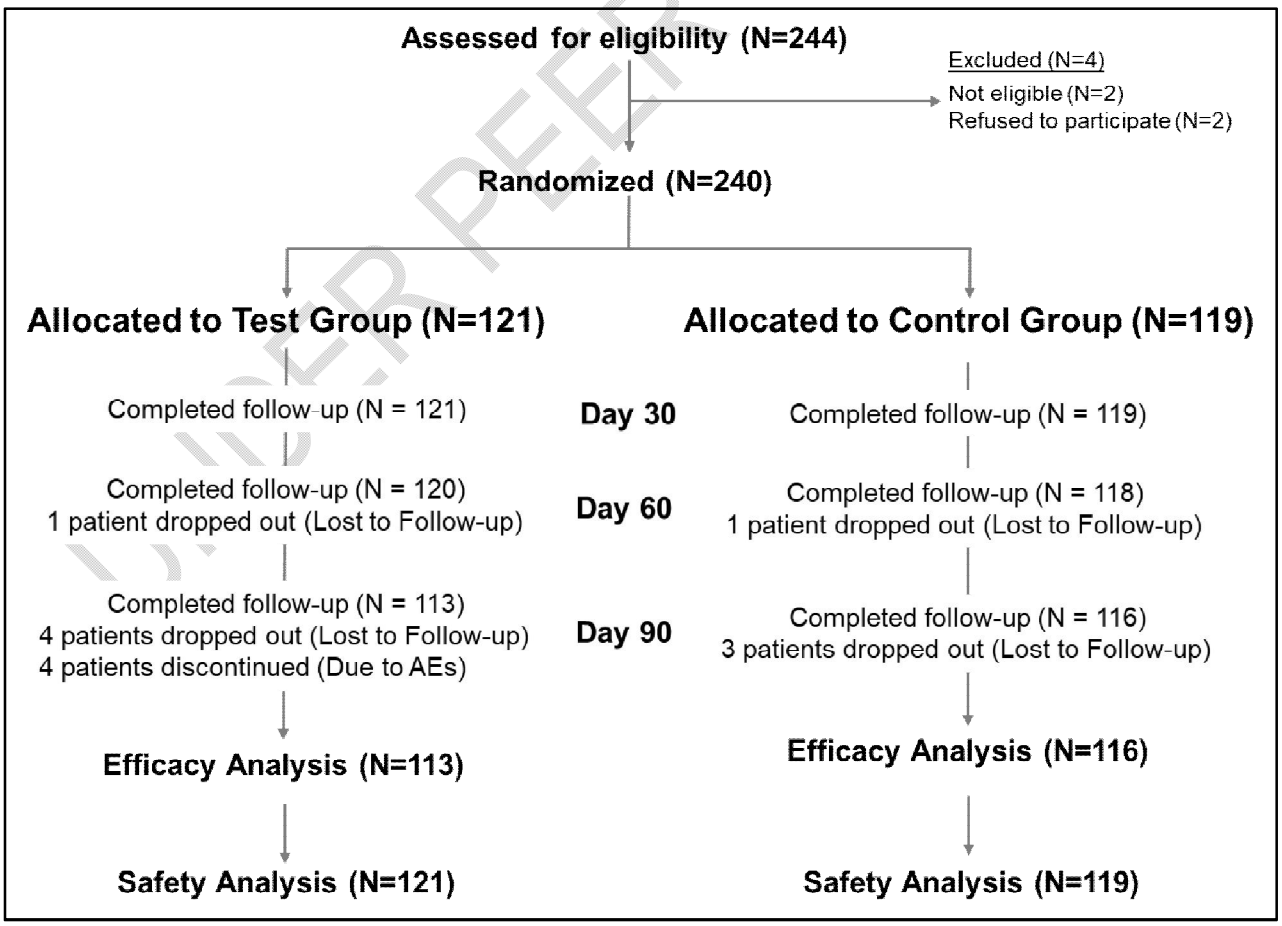

Figure 1: Disposition of patients in the study

2.3 Interventions

Eligible patients were randomly assigned using block randomization in a ratio of 1:1 to the E+S(-)M or C+M group. The assigned treatment arm was not known to the site staff, investigator and patients. Allocation concealment was done by sealed sequentially numbered opaque envelopes. The patients assigned to the E+S(-)M group received FDC of Efonidipine 40 mg and S (-) Metoprolol 25 mg tablet and the C+M group received FDC of Cilnidipine 10 mg and Metoprolol 50 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 treatment duration was 90 days 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 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 90 from baseline for comparison within the individual treatment group. The 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

During the period December 2020 - August 2021, 240 eligible patients were enrolled and randomized to receive either E+S(-)M or C+M treatment in a 1:1 ratio. The mean age of the population was 47.83 (range 22-73) years. A total of 58% of patients were diagnosed with Stage I hypertension and 42% with Stage II hypertension at the time of enrolment. Criteria for categorizing these patients were predefined and as per JNC VII hypertension guidelines. At baseline, patients from both 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+S(-)M (Mean ± SD)	C+M (Mean ± SD)	p value*
N		121	119	-
Age, years		48.03 ± 11.37	47.64 ± 10.94	0.79
Gender (n, %)				
Male		68 (56.20)	60 (50.42)	0.370[#]
Female		53 (43.80)	59 (49.58)	
Height, cm		161.40 ± 9.15	160.35 ± 8.08	0.34
Weight, kg		63.26 ± 9.56	63.54 ± 10.03	0.82
Body mass index, kg/m^2		24.25 ± 2.89	24.71 ± 3.48	0.26
Heart Rate, beats/min		80.02 ± 8.20	80.59 ± 8.21	0.59
Respiratory Rate, breaths/min		17.35 ± 1.98	17.30 ± 1.95	0.96
Blood Pressure				
Stage I	**SBP, mmHg**	146.85 ± 5.38 (n=70)	146.94 ± 5.02 (n=69)	0.92
	DBP, mmHg	93.12 ± 2.84 (n=70)	93.50 ± 3.01 (n=69)	0.45
Stage II	**SBP, mmHg**	164.15 ± 9.16 (n=51)	164.33 ± 8.35 (n=50)	0.92
	DBP, mmHg	105.50 ± 7.41 (n=51)	106.10 ± 8.20 (n=50)	0.70
All patients	**SBP, mmHg**	154.14 ± 11.18	154.24 ± 10.85	0.94
	DBP, mmHg	98.34 ± 8.07	98.79 ± 8.50	0.67

**Unpaired t-test*
[#]Pearson chi^2 test

3.2 Primary Endpoint

3.2.1 Reduction in Blood Pressure at Day 90

After 90 days of E+S(-)M treatment, SBP reduced from 154.60 ± 11.33 mmHg to 123.59 ± 15.21 mmHg ($p < 0.0001$) with a mean difference of 31.01 mmHg and DBP reduced from 98.68 ± 8.18 mmHg to 82.38 ± 5.05 mmHg ($p < 0.0001$) with a mean difference of 16.29 mmHg (Table 2 and 3).
It was noted that by the end of the treatment phase there was no statistically significant difference in mean change SBP ($p = 0.88$) and DBP ($p = 0.75$) between the two groups.

Table 2: Reduction in Systolic Blood Pressure from baseline at Day 90

	E+S(-)M (Mean ± SD)	C+M (Mean ± SD)	Change in SBP Control vs. test
Baseline	154.60 ± 11.33	154.28 ± 10.71	-
	**p = 0.83 (comparison between groups)		
Day 90	123.59 ± 15.21	123.74 ± 14.86	**p = 0.88 Mean Diff = -0.46 95% CI = -6.51, 5.59
	*p <0.0001 (Change from Baseline)	*p <0.0001 (Change from Baseline)	
	Mean Difference (95% CI) 31.01 ± 23.38 (26.65, 35.37)	Mean Difference (95% CI) 30.55 ± 23.08 (26.30, 34.79)	
	**p = 0.94 (comparison between groups)		

**Paired t-test*
***Unpaired t-test*
E+S(-)M: FDC of Efonidipine 40 mg + S (-) Metoprolol 25 mg tablet
C+M: FDC of Cilnidipine 10 mg + Metoprolol 50 mg tablet

Table 3: Reduction in Diastolic Blood Pressure from baseline at Day 90

	E+S(-)M (Mean ± SD)	C+M (Mean ± SD)	Change in DBP Control vs. test
Baseline	98.68 ± 8.18	98.95 ± 8.55	-
	**p = 0.81 (comparison between groups)		
Day 90	82.38 ± 5.05	82.21 ± 5.03	**p = 0.75 Mean Diff = 0.45 95% CI = -2.34, 3.22
	*p <0.0001 (Change from Baseline)	*p <0.0001 (Change from Baseline)	
	Mean Difference (95% CI) 16.29 ± 10.52 (14.33, 18.26)	Mean Difference (95% CI) 16.74 ± 10.80 (14.75, 18.72)	

	**p = 0.79 (comparison between groups)	

**Paired t-test*
***Unpaired t-test*
E+S(-)M: FDC of Efonidipine 40 mg + S (-) Metoprolol 25 mg tablet
C+M: FDC of Cilnidipine 10 mg + Metoprolol 50 mg tablet

The efficacy of study treatments was evaluated in terms of non-inferiority between the two treatment groups. The margin of non-inferiority was set to 10mmHg. The difference in systolic blood pressure between the E+S(-)M and C+M was -0.46 (95%CI: -6.51 to 5.59) and the difference in diastolic blood pressure was 0.45 (p=0.75; 95% CI: -2.34 to 3.22). The boundary of the 95% CI was below the margin of 10 mmHg, confirming the non-inferiority of the E+S(-)M treatment to the C+M treatment.

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+S(-)M 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 14.31 and 9.36 mm Hg in patients with Stage I hypertension, and by 52.05 and 25.03 mm Hg in patients with Stage II hypertension (Table 4). 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*=0.80; Stage II *p*=0.73) and DBP (Stage I *p*=0.70; Stage II *p*=0.47).

Table 4: Reduction in Blood Pressure from baseline at Day 90 in Stage I and Stage II hypertensive patients with E+S(-)M treatment

Blood Pressure	Baseline	Day 90	Mean difference	*p* Value*
Stage I (N=63)				
SBP (mmHg)	146.94 ± 5.43	132.63 ± 7.39	14.31 ± 9.30 (11.97, 16.65)	<0.0001
DBP (mmHg)	93.19 ± 2.77	83.83 ± 5.00	9.36 ± 5.22 (8.05, 10.67)	<0.0001
Stage II (N=50)				
SBP (mmHg)	164.27 ± 9.24	112.20 ± 14.91	52.05 ± 18.17 (48.50, 58.04)	<0.0001
DBP (mmHg)	105.59 ± 7.46	80.56 ± 4.53	25.03 ± 8.88 (23.77, 28.90)	<0.0001

**Paired t-test, Values are in mean ± standard deviation, 95%CI is given with mean difference*

3.3 Secondary Endpoints

3.3.1 Target Blood pressure

After 30 days of E+S(-)M treatment, 79% of patients had achieved the target BP of <140/90 mmHg, and almost 83% were controlled after 2 months of E+S(-)M treatment (Day 60). Additionally, after 3 months of treatment, 95% of patients achieved target BP demonstrating uniform efficacy of the E+S(-)M regimen. Table 5 presents details of the number of patients achieving the target goal of <140/90 mmHg.

Table 5: Number of patients achieved target BP goal with E+S(-)M treatment

Study population	Day 30 N(%)	Day 60 N(%)	Day 90 N(%)
All trial population	95/121 (78.51)	99/120 (82.5)	107/113 (94.69)
Stage I Hypertension	45/70 (64.28)	58/69 (84.06)	59/63 (93.65)
Stage II Hypertension	45/51 (88.24)	47/51 (92.16)	48/50 (96.00)

3.3.2 Blood pressure reduction at Day 30

In the E+S(-)M group, the SBP reduced from 154.14 ± 11.18 mmHg to 136.06 ± 10.55 mmHg with the mean reduction of 18.09 and the DBP reduced from 98.34 ± 8.07 mmHg to 86.68 ± 5.51 mmHg with the mean reduction of 11.66 mmHg at Day 30 (Table 6). The reduction in the average 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 change SBP (p =0.66) and DBP (p =0.67).

Table 6: Reduction in Blood Pressure from baseline to day 30 with E+S(-)M treatment

Blood Pressure	Baseline	Day 30	Mean difference	*p* Value*
Overall population (N=121)				
SBP (mmHg)	154.14 ± 11.18	136.06 ± 10.55	18.09 ± 14.36 (15.50, 20.67)	<0.0001
DBP (mmHg)	98.34 ± 8.07	86.68 ± 5.51	11.66 ± 9.77 (9.90, 13.42)	<0.0001
Stage I (N=70)				
SBP (mmHg)	146.85 ± 5.34	136.73 ± 9.20	10.12 ± 8.10 (8.19, 12.05)	<0.0001
DBP (mmHg)	93.12 ± 2.84	86.78 ± 5.99	6.35 ± 6.09 (4.91, 7.79)	<0.0001
Stage II (N=51)				

SBP (mmHg)	164.15 ± 9.18	135.13 ± 12.21	29.02 ± 13.90 (25.11, 32.93)	<0.0001
DBP (mmHg)	105.50 ± 7.41	86.54 ± 4.82	18.95 ± 9.23 (16.36, 21.55)	<0.0001

**Paired t-test*

Values are in mean ± standard deviation, 95%CI is given with mean difference

3.3.2 Blood pressure reduction at Day 60

In the E+S(-)M group, the SBP reduced from 154.26 ± 11.15 mmHg to 129.48 ± 10.51 mmHg at Day 60 with the mean reduction of 24.78 and the DBP reduced from 98.34 ± 8.11 mmHg to 84.17 ± 5.51 mmHg at Day 60 with the mean reduction of 25.16 (Table 7). The reduction in the average 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 change SBP (p =0.84) and DBP (p =0.63) between the two groups.

Table 7: Reduction in Blood Pressure from baseline to day 60 with E+S(-)M treatment

Blood Pressure	Baseline	Day 60	Mean difference	*p* Value*
Overall population (N=120)				
SBP (mmHg)	154.26 ± 11.15	129.48 ± 10.51	24.78 ± 17.21 (21.67, 27.89)	<0.0001
DBP (mmHg)	98.34 ± 8.11	84.17 ± 5.51	14.17 ± 10.23 (12.32, 16.02)	<0.0001
Stage I (N=69)				
SBP (mmHg)	146.95 ± 5.31	133.34 ± 8.21	13.61 ± 8.71 (11.52, 15.70)	<0.0001
DBP (mmHg)	93.06 ± 2.80	84.72 ± 6.14	8.34 ± 6.04 (6.89, 9.80)	<0.0001
Stage II (N=51)				
SBP (mmHg)	164.15 ± 9.18	124.26 ± 11.08	39.90 ± 14.04 (35.95, 43.84)	<0.0001
DBP (mmHg)	105.50 ± 7.41	83.44 ± 4.47	22.06 ± 9.44 (19.41, 24.72)	<0.0001

**Paired t-test*

Values are in mean ± standard deviation, 95%CI is given with mean difference

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 79.64 ± 7.71 bpm to 76.11 ± 5.89 bpm (p =0.0002) in patients treated with E+S(-)M intervention. Similar results were observed for the C+M treatment. No statistically significant difference was observed in the reduction of the heart rate (p = 0.68) when the two treatment groups were compared.

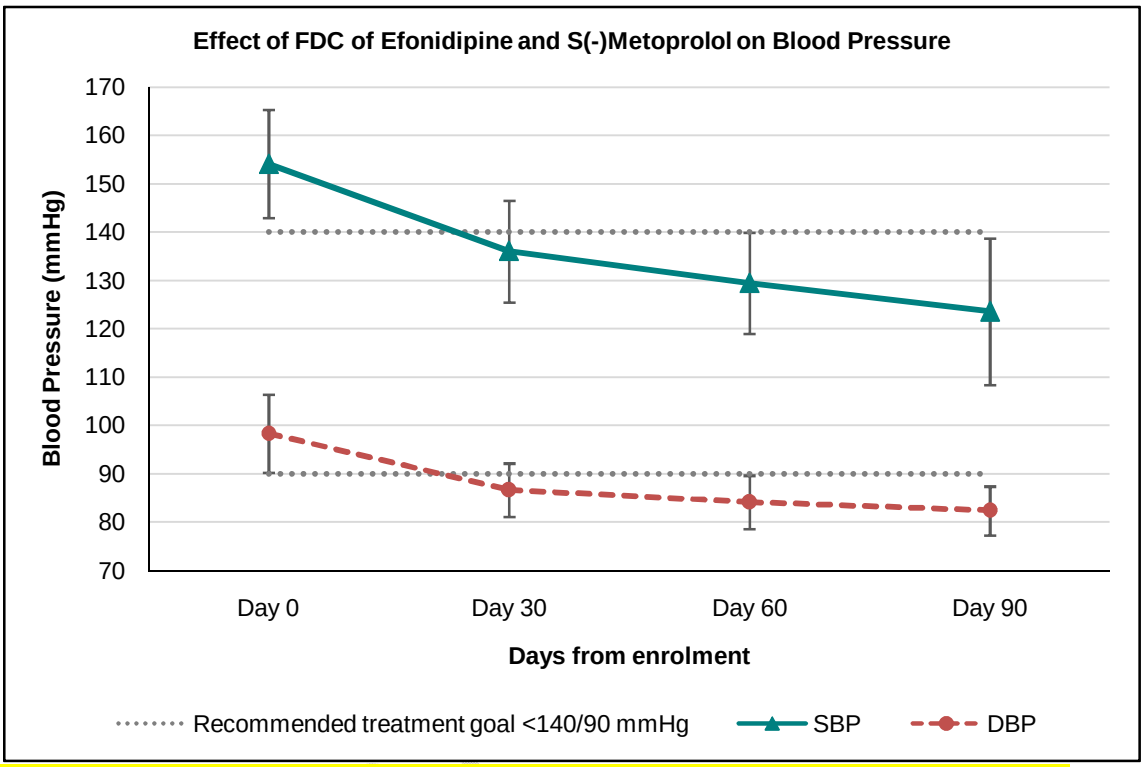

Figure 2: Reduction in Systolic and Diastolic Blood Pressure after E+S(-)M treatment

3.3.4 Analysis of Adverse events (AEs)

Safety was evaluated based on the incidences of AEs reported during the study. There were 18 AEs reported in 13 patients during the study period. In the E+S(-)M group, 6 AEs (headache, vomiting, fever, low blood pressure, decrease in heartbeat and skin redness) were reported in 7 patients whereas 4 AEs (headache, back pain, dizziness, vertigo, diarrhea) were reported in 6 patients in the C+M group. All adverse events were mild to moderate in severity. Four patients of the E+S(-)M group were discontinued from the study due to AEs experienced. At the end of the study, all AEs were resolved without any sequelae. A total of 5.78% patients reported AEs in the E+S(-)M group whereas 5.04% in C+M group (p=0.80). Both the investigational products were well tolerated by the patients on administration as a single tablet 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, eGFR, blood urea nitrogen, total bilirubin, SGOT, SGPT were assessed before the start of the treatment and after completion of E+S(-)M treatment (day 90). Details of laboratory tests are shown in Table 8.

Table 8: Changes in laboratory parameters with E+S(-)M treatment

Laboratory parameters	At baseline	At day 90
Serum Creatinine (mg/dL)	0.88 ± 0.19	0.94 ± 0.24
eGFR (ml/min/1.73m^2)	87.11 ± 23.07	88.91 ± 21.27
BUN (mg/dL)	11.71 ± 3.10	11.87 ± 3.40
Total Bilirubin (mg/dL)	0.63 ± 0.27	0.64 ± 0.20
SGOT (IU/L)	32.07 ± 13.38	32.09 ± 11.54
SGPT (IU/L)	33.12 ± 22.24	31.03 ± 20.92

Values are in mean ± standard deviation

4. DISCUSSION

A substantial decrease in cardiovascular complications can be achieved even with small reductions in blood pressure. [19] "Successful antihypertensive therapy depends on the efficacy of the therapeutic agents and also its safety or its effect on the patient's well-being. Combining multiple classes of antihypertensive drugs together is one of the most important factors for achieving blood pressure control in most hypertensive patients. The benefits of combination therapy in comparison with monotherapy include enhancement of each drug's hypertensive effects and a potential reduction of side effects if each drug is used at a lower dose". [20] A beneficial role for the FDC of Efonidipine and S(-) Metoprolol in the management of hypertension can be established based on the findings from the current study.

"The mechanisms that lead to a blood pressure increase in a patient are diverse- monotherapy acts on one or at best two of these mechanisms, while the use of a combination of drugs allows for action on several different hypertensive mechanisms". [21] The E+S(-)M is a unique combination of Efonidipine, a dual L- and T-type dihydropyridine Ca^{2+} channel blocker and S-Metoprolol, a chirally pure form of racemate metoprolol, a beta blocker. Owing to the distinctive mechanism of action of the E+S(-)M combination, the study results demonstrated a significant decrease in the SBP and DBP after the completion of the treatment phase compared to the baseline. It was illustrated from the results that the mean reduction in SBP was 31.01 mmHg and DBP was 16.29 mmHg at Day 90. A double-digit reduction in blood pressure was evident after only 30 days of administration. Early

restoration of BP could be one of the important determinants to improve cardiovascular progress in patients with hypertension.

Recent clinical trials suggest that the approach of using monotherapy for the control of hypertension is not likely to be successful in most patients and especially in those with some comorbidities. To achieve target BP goals, typically 2 or more medications are required. [19, 22, 23, 24] The use of combination drugs as the first-line treatment reduces the gap between antihypertensive use and the achievement of the BP target goal. [25] Most national and international hypertension guidelines recommend a target BP of less than 140/90 mmHg. [12,27] In this study, the E+S(-)M combination achieved the treatment goal as early as week 4 (79%) and majority of the patients (95%) achieved BP response at the end of the study phase.

In addition to the usage of fixed-dose combinations, the selection of suitable combinations is based on the patient's preference, treatment adherence, and compliance. [26] The initial use of antihypertensive drugs in combination promotes BP reduction, reduces the heterogeneity of the BP response between patients [27], and also reduces the risk of cardiovascular events by 15 percent in the high-risk group or aged fifty-five or older. [28]

The FDC of Efonidipine and S(-)Metoprolol significantly decreased ($p=0.0002$) the heart rate up to 76.11 (± 5.89) bpm in the present study. It has been reported that bradycardia depends on stimulation and frequency; i.e. inhibitors of heart rate are more dramatically effective when the heart rate is initially high. [29] Efonidipine was shown to have frequency-dependent inhibitory effects on myocardial T-type Ca^{2+} and had no negative chronotropic action when the heart rate was below 70 bpm. Efonidipine significantly decreased heart rate in patients with basal rate higher than 80 bpm while no significant change was observed in patients with basal rate between 70 and 80 bpm. [30] Furthermore, beta-blockers antagonize the possible dihydropyridines-induced reflex sympathetic activation. [31] Thus, in the present study, heart rate significantly decreased after administration of E+S(-)M combination, but there was no marked reduction below the normal level. This normalization of heart rate results in reduced oxygen consumption and is favorable for the long-term maintenance of myocardial function.

"Given that the cardiovascular disease burden is on the rise, continuing to plan, develop, and implement more innovative strategies to improve clinical outcomes in all areas of the prevention, diagnosis, and treatment spectrum of hypertension is paramount. 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". [32]

5. CONCLUSION

In conclusion, the current study findings suggest that fixed-dose combination therapy of Efonidipine 40 mg + S(-)Metoprolol 25 mg resulted in clinically significant improvement in blood pressure control and 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

ALL PATIENTS PROVIDED WRITTEN INFORMED CONSENT TO PARTICIPATE IN THE STUDY.

ETHICAL APPROVAL

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/2020/12/029740).

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