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Original Article

TO EVALUATE THE SAFETY AND EFFICACY OF AMLODIPINE AND CHLORTHALIDONE IN COMBINATION WITH TELMISARTAN IN HYPERTENSIVE PATIENTS ATTENDING TERTIARY CARE CENTRE, TELANGANA

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ABSTRACT

Objective: The main objective of this study is to evaluate and compare the effects of both treatments on systolic and diastolic blood pressure in 4th, and 8th weeks with baseline

Methods: A prospective, comparative, Open-label, and parallel-group clinical study was conducted in out patient's department of general medicine at Osmania general hospital. 120 patients were randomly allocated into 2 groups. Group 1 with 60 patients received Tab: Telmisartan 40 mg+Amlodipine 5 mg once daily, and Group 2 with 60 patients received Tab: Telmisartan 40 mg+ Chlorthalidone 6.25 mg once daily for a period of 8 w. Follow-up was done in the 4th week and 8th week to evaluate the safety and efficacy in hypertensive patients.

Results: The differences in the SBP, DBP, and HR in group A (P value<0.001) and group B (P value<0.001) at the 4th week and 8th week follow-up periods with baseline value (0 w) were statistically significant as P value<0.05.

Conclusion: The combination of telmisartan plus amlodipine is equally effective as the combination of telmisartan plus chlorthalidone in decreasing SBP, DBP, HR, and MAP. No major adverse drug reactions were noted during the study period.

Keywords: Hypertension, Telmisartan, Amlodipine, Chlorthalidone

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INTRODUCTION

Hypertension is one of the leading worldwide public health challenges. Suggested reports say that the prevalence of hypertension is rapidly increasing in developing countries and is one of the major causes of mortality and morbidity [1]. The increasing worldwide prevalence of hypertension is attributed mainly to population growth, aging, and behavioral risk factors i.e., unhealthy diet, harmful use of alcohol and tobacco, lack of physical activity, excess weight, and persistent stress [2].

Hypertension accounts for 35% of cerebrovascular diseases and 21% of ischemic heart diseases, suggesting the importance of hypertension management because it means that 35% of cerebrovascular diseases and 21% of ischemic heart diseases are preventable if normal blood pressure (BP) could be maintained in the population [3].

WHO rates hypertension as one of the most important causes of premature death worldwide. Prevalence (GLOBAL PREVALENCE) of hypertension varies regionally. In India, the prevalence of hypertension is 33% in the urban population and 25% in the rural population. The prevalence of hypertension in south India is 31.8% in urban and 21.1% in rural populations. Hypertension is directly responsible for 24% of all CHD deaths and 57% of all stroke deaths in India [4]. Despite the advances in hypertension management and emphasis on patient education, hypertension continues to be a significant health burden [5].

As it showed, no symptoms Hypertension is known as a silent killer. hypertension Usually can be controlled by a healthy diet, regular exercise, medication prescribed by doctors, or a combination of these. Hypertension if untreated, will cause serious conditions [7]. It is associated with cardiovascular disease, obesity, insulin resistance, carbohydrate tolerance, atherosclerosis, and hyperuricemia. Hypertension affects the structures and functions of various target organs, including the kidney, brain, and eye, related to the end stage of renal disease and is the cause of stroke [8].

Hypertension is not easily controlled with only a single agent unless it is mild, and dual combination therapy is recommended from the first for patients with stage 2 or higher hypertension or high-risk patients [3].

The combined effect of dual therapy provides not only hypotensive action but also greater prevention of hypertension consequences. In addition, the use of concomitant drugs with different mechanisms of action can offset the potential adverse effects (AEs) of each drug. In this context, various types of fixed-dose combinations have recently been developed and used, revealing improved patient adherence to their convenient regimen [6].

A hypertension management schedule involving (BP)/Cholesterol-lowering drugs and lifestyle changes for a period of 60 d showed that combination drug therapy was more effective than immunotherapies of the same drugs used at higher dosages [9]. Various types of fixed-dose combinations have recently been developed and used, revealing improved patient adherence to their convenient regimen [6].

The 2007 European Society of Hypertension/European Society of Cardiology guidelines for the management of hypertension introduced combination therapies with ACEIs and ARBs, such as ACEI/diuretic, ARB/diuretic, CCB/ARB, and CCB/ACEI, which are superior to other combination therapies [3]. Telmisartan, a commonly used angiotensin receptor blocker, plays a role in the treatment of hypertension by RAAS-blocking activity. Amlodipine, CCB acts by inhibiting L-type calcium channels. Chlorthalidone, (non-benzothiadiazides) diuretic is used nowadays for hypertension treatment [12]. ACEIs/ARBs were the most commonly used drugs for monotherapy, in 2+therapy, the most common add-on drug was a diuretic and in combination therapy, the most common combination was ACE/ARB+Diuretics [11].

Combination therapy with a renin-angiotensin system (RAS) inhibitor (either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker [ARB] plus a diuretic is a widely used and effective

approach that has become an accepted component of evidence-based hypertension treatment guidelines [10]. The combination of an angiotensin II receptor blocker with a thiazide diuretic is efficacious and well-tolerated in numerous clinical trials. This combination could be of particular value in hypertensive patients with additional cardiovascular risk factors or in populations whose BP is traditionally poorly controlled, such as elderly persons with diabetes [6].

This study evaluates the efficacy of amlodipine and chlorthalidone in Combination with telmisartan in hypertensive patients attending a tertiary care centre, in Telangana.

MATERIALS AND METHODS

A prospective, comparative, Open-label, and parallel-group clinical study was conducted in out patient's department of general medicine at Osmania general hospital. Patients in the age group of 20 to 60 y of both genders, who were diagnosed with hypertension with Systolic BP (SBP)>139 mmHg and<180 mmHg and Diastolic BP(DBP)>89 mmHg and<110 mmHg and Subjects who were resistant to monotherapy-either amlodipine or Chlorthalidone alone were included in the study. Patients with age<2 y, Pregnant and breastfeeding mothers, with cerebrovascular disease, ischaemic heart disease, congestive cardiac failure, cardiac arrhythmia, liver impairment, and renal failure were excluded from the study.

After the selection of the patients based on the above criteria, the study was explained to the patient in his comprehensible language, and written informed consent was obtained. After initial screening, demographic data, medical history, findings of physical examination, and clinical examination were recorded in the case report form. 120 patients were randomly allocated into 2 groups.

Group 1: 60 patients received Tab: Telmisartan 40 mg+Amlodipine 5 mg once daily for a period of 8 w.

Group 2: 60 patients received Tab: Telmisartan 40 mg+Chlorthalidone 6.25 mg once daily for a period of 8 w.

Follow-up was done. SBP, DBP, and HR were recorded at baseline and 4th week, 8th week, MAP, Serum electrolytes levels were recorded at baseline and 4th week, and 8th week. Any adverse effects of the treatment were also recorded.

Statistical methods

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. For normally distributed Quantitative parameters the mean values were compared between study groups using an independent sample t-test (2 groups). For non-normally distributed Quantitative parameters, Medians and Interquartile range (IQR) were compared between study groups using Mann Whitney u test (2 groups). The change in the quantitative parameters, before and after the intervention, was assessed by paired t-test. Categorical outcomes were compared between study groups using the Chi-square test/Fisher's Exact test (If the overall sample size was<20 or if the expected number in any one of the cells is<5, Fisher's exact test was used). P value<0.05 was considered statistically significant. Data were analyzed by using SPSS software, V.22.

Ethical clearance

Ethical clearance was obtained from the Institutional Ethical Committee, Department of Pharmacology, Osmania Medical College, Koti, Hyderabad bearing the number Ref. No. ECR/300/ Inst/AP/2013/RR-19.

RESULTS AND DISCUSSION

The study was conducted at the Department of General medicine, Osmania General Hospital, Hyderabad. The study was started after getting written approval from Osmania Medical College, Institutional Ethics Committee, and patients were enrolled after getting written informed consent.

All the patients with hypertension as per inclusion criteria, were enrolled and randomly divided into two groups.

A total of 120 subjects were included in the final analysis.

The age and gender distribution of the study population are given below:

Table 1: Comparison of age and gender distribution of patients between group1 and 2

Gender	Study group		P value
	Group 1 (N=60)	Group 2(N=60)	
Age (in years) (mean±SD)	52.78±4.04	53.12±4.75	0.680
Gender			
Male	38 (63.33%)	29 (48.33%)	0.098
Female	22 (36.67%)	31 (51.67%)	

The mean age (in years) was 52.78±4.04 in group 1 and it was 53.12±4.75 in group 2; the mean difference between the two groups was statistically not significant (P value 0.680). In group 1, 38 (63.33%) participants were male and 22 (36.67%) participants were female. In group 2, 29 (48.33%) participants were male and 31 (51.67%) participants were female. The difference in the proportion of gender between the study group was statistically not significant (P value 0.098).

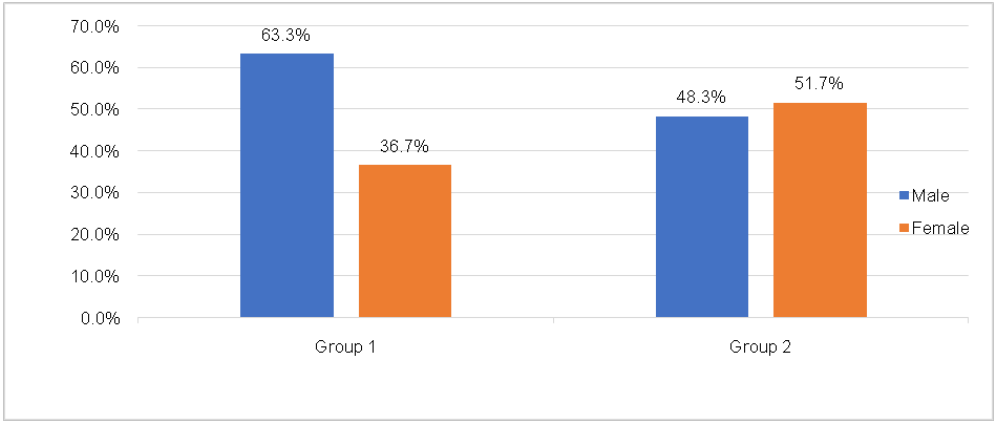

Fig. 1: Cluster bar chart of comparison of gender between study groups (N=120)

Table 2: Comparison of mean of vital signs parameters in pre-operative and different follow-up periods in study groups individually

	Periods		
	0 w	**4th week**	**8th week**
	Group one (N=60)		
SBP (mmHg)	162.68±11.21	154.6±10.22	147.28±7.94
P value	(baseline)	<0.001	<0.001
DBP (mmHg)	103.37±5.06	100.35±4.75	94.58±4.21
P value	(baseline)	<0.001	<0.001
HR (beats/mints)	83.73±10.11	80.48±10.09	79.63±10.48
P value	(baseline)	0.003	0.002
MAP (mmHg)	86.58±9.5	*	85.5±9.23
P value	(baseline)	*	0.525
	Group two(N=60)		
SBP (mmHg)	163.72±10.62	154.33±10.23	146.47±7.41
P value	(baseline)	<0.001	<0.001
DBP (mmHg)	101.65±6.27	99.35±5.43	94.27±4.52
P value	(baseline)	<0.001	<0.001
HR (beats/mints)	84.38±12.03	83.43±13.07	82.35±14.61
P value	(baseline)	0. 004	0. 003
MAP (mmHg)	86.27±9.32	*	84.63±8.87
P value	(baseline)	*	0.302

(In table 2 SBP, DBP, and HR have P values<0.05 which are statistically significant in groups 1 and 2)

Among people in group 1, the mean systolic blood pressure was 162.68±11.21in 0 w, 154.6±10.22 at 4th-week follow-up, and 147.28±7.94 at 8thweek follow-up. The differences in the systolic blood pressure at the 4th week and 8th week follow-up periods with baseline value (0 w) were statistically significant (P value<0.05). The mean diastolic blood pressure was 103.37±5.06 in 0 w, 100.35±4.75 at 4th-week follow-up and 94.58±4.21 at 8th-week follow-up. The differences in the diastolic blood pressure at the 4th week and 8th week follow-up periods with baseline value (0 w) were statistically significant (P value<0.05). The mean heart rate was 83.73±10.11in 0 w, 80.48±10.09 at 4th-week follow-up and79.63±10.48 at 8thweek follow-up. The differences in the heart rate at the 4th week and 8th week follow-up periods with baseline value (0 w) were statistically significant (P value<0.05). The mean MAP was 86.58±9.5 in 0 w and 85.5±9.23 at the 8thweek follow-up. The differences in the MAP at 8th week follow-up periods with baseline value (0 w) were statistically not significant (P value>0.05).

Among people in group 2, the mean systolic blood pressure was 163.72±10.62 in 0 w, 154.33±10.23 at the 4th week follow up and146.47±7.41at 8thweek follow-up. The differences in the systolic blood pressure at the 4th week and 8th week follow-up periods with baseline value (0 w) were statistically significant (P value<0.05). The mean diastolic blood pressure was 101.65±6.27 in 0 w, 99.35±5.43 at the 4th-week follow-up, and 94.27±4.52 at the 8thweek follow-up. The differences in the diastolic blood pressure at the 4th week and 8th week follow-up periods with baseline value (0 w) were statistically significant (P value<0.05). The mean heart rate was 84.38±12.03 in 0 w, 83.43±13.07 at the 4th week follow-up, and 82.35±14.61 at the 8thweek follow-up. The differences in the heart rate at the 4th week and 8th week follow-up periods with baseline value (0 w) were statistically significant (P value<0.05). The mean MAP was 86.27±9.32 in 0 w and 84.63±8.87 at the 8thweek follow-up. The differences in the MAP at 8th week follow-up periods with baseline value (0 w) were statistically not significant (P value>0.05).

Table 3: Comparison of mean of serum electrolytes parameters in pre-operative and different follow-up periods among groups one and two (N=60)

	Group one		Group two	
	0 w	**8th week**	**0 w**	**8th week**
Na (mEq/l)	136.69±5.15	135.02±5.86	134.61±3.97	133.77±6.19
P value	(baseline)	0.089	(baseline)	0.391
K (mmol/l)	3.92±0.62	4.40±0.61	3.82±0.57	4.46±0.46
P value	(baseline)	0.061	(baseline)	0.071
mg (mg/dl)	2.04±0.39	2.07±0.03	2.02±0.27	2.06±0.03
P value	(baseline)	0.646	(baseline)	0.262
Ca (mg/dl)	9.56±0.56	9.53±0.53	9.56±0.59	9.51±0.60
P value	(baseline)	0.152	(baseline)	0.270
Cl (mEq/l)	105.12±3.89	103.2±8.96	106.55±4.75	104.62±7.9
P value	(baseline)	0.078	(baseline)	0.069

(In table 3, the P value is not statistically significant in groups 1 and 2)

Among people in group 1, the mean Na (mEq/l) was 136.69±5.15 in 0 w and 135.02±5.86 at the 8th week follow-up. The differences in the Na (mEq/l) at 8th week follow-up periods with baseline value (0 w) were statistically not significant (P value>0.05). The mean K (mmol/l) was 3.92±0.62 in 0 w and 4.40±0.61 at the 8thweek follow-up. The differences in the K (mmol/l) at 8th week follow-up periods with baseline value (0 w) were not statistically significant (P value>0.05). The mean mg (mg/dl) was 2.04±0.39 in 0 w and 2.07±0.03 at the 8th week follow-up. The differences in the mg (mg/dl) at 8th week follow-up periods with baseline value (0 w) were statistically not significant (P value>0.05). The mean Calcium (mg/dl) was 9.56±0.56 in 0 w and 9.53±0.53 at the 8th week follow-up. The differences in the ca (mg/dl) at 8th week follow-up periods with baseline value (0 w) were statistically not significant (P value>0.05). The mean Cl (mEq/l) was 105.12±3.89 in 0 w and 103.2±8.96 at the 8thweek follow-up. The differences in the Cl (mEq/l) at 8th week follow-up periods with baseline value (0 w) were statistically not significant (P value>0.05).

Among people in group 2, the mean Na (mEq/l) was 134.61±3.97 in 0 w and 133.77±6.19 at the 8thweek follow-up. The differences in the Na (mEq/l) at 8th week follow-up periods with baseline value (0 w) were

statistically not significant (P value>0.05). The mean K (mmol/l) was 3.82±0.57 in 0-week and 4.46±0.46 at 8th week follow-up. The differences in the K (mmol/l) at 8th week follow-up periods with baseline value (0 w) were statistically not significant (P value>0.05). The mean mg (mg/dl) was 2.02±0.27 in 0 w and 2.06±0.03 at the 8th week follow-up. The differences in the mg (mg/dl) at 8th week follow-up periods with baseline value (0 w) were statistically not significant (P value>0.05). The mean Ca (mg/dl) was 9.56±0.59 in 0 weeks and 9.51±0.60 at the 8thweek follow-up. The differences in the Ca (mg/dl) at 8th week follow-up periods with baseline value (0 w) were statistically not significant (P value>0.05). The mean Cl (mEq/l) was 106.55±4.75 in 0 w and 104.62±7.9 at the 8th week follow-up. The differences in the Cl (mEq/l) at 8th week follow-up periods with baseline value (0 w) were statistically not significant (P value>0.05) (table 3).

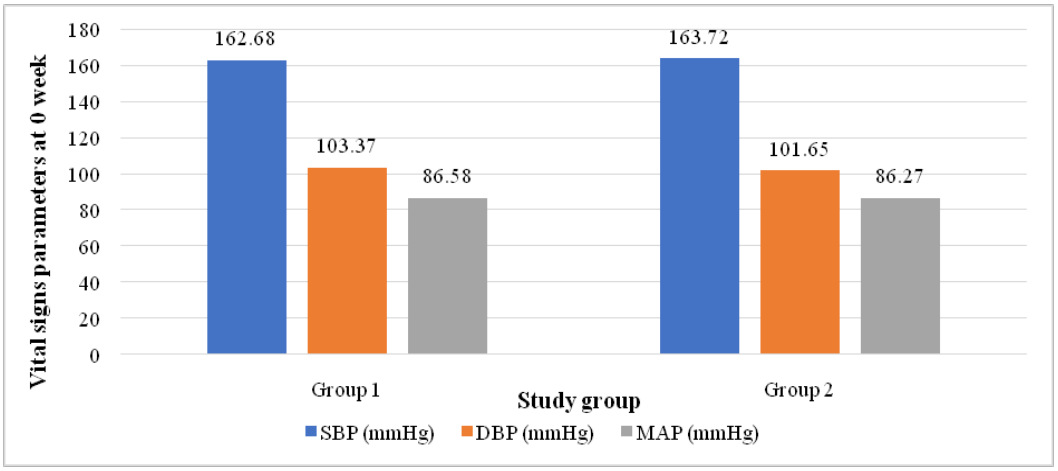

Fig. 2: Comparative bar chart of the mean of vital signs parameters at 0 w between group 1 and group 2

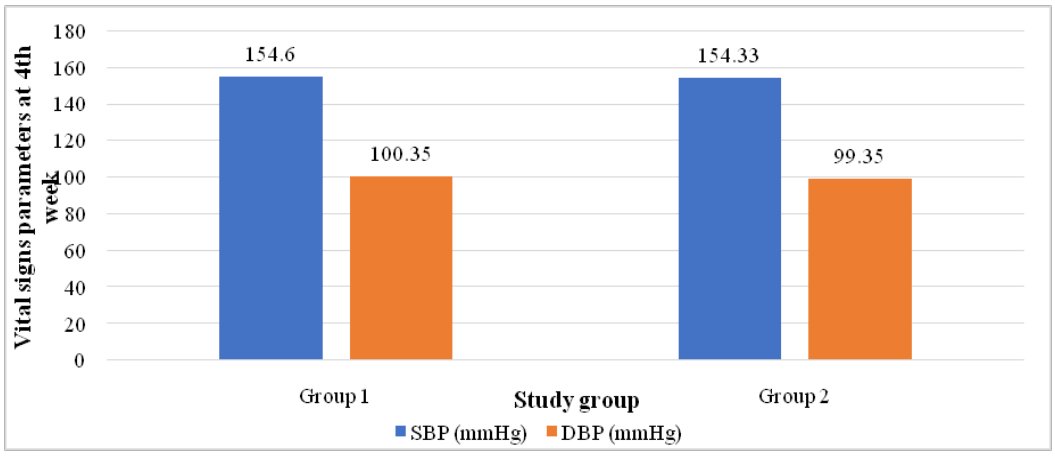

Fig. 3: Comparative bar chart of the mean of vital signs parameters at the 4th week between group 1 and group 2

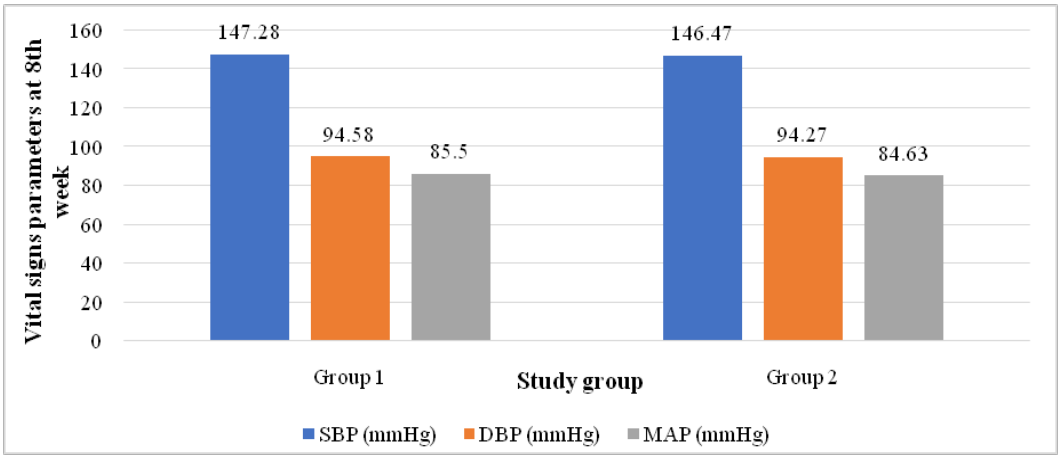

Fig. 4: Comparative bar chart of the mean of vital signs parameters at the 8th week between group 1 and group 2

Table 4: Adverse effects in two groups

	Group 1 (N=60)	Group 2 (N=60)	Fisher exact P value
Headache	6 (10%)	3 (5%)	0.491
Dizziness	2 (3.33%)	2 (3.33%)	1.000
Nausea	3 (5%)	2 (3.33%)	1.000
Pedal edema	1 (1.67%)	0 (0%)	*
Diarrhea	0 (0%)	2 (3.33%)	*

(In table 4, the P value is not statistically significant)

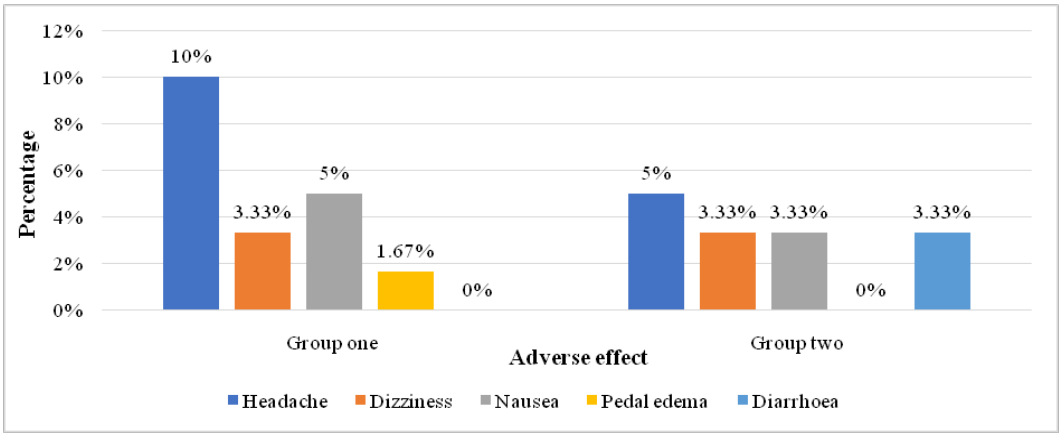

Fig. 5: Clustered bar chart of adverse effects in two groups

At the end of 8 w of treatment, the incidence of adverse effects recorded in both groups showed that the adverse effects were less in group2 compared to group 1. Headache was noted in 6 patients in group1 and 3 patients in group 2.

Dizziness was seen in 2 patients of group 1 and 2 patients of group2. Diarrhea was complained by 2 patients in group 2 and none in group 1. One patient from group 1 and none from group 2 complained of pedal edema. Nausea was seen in 3 patients in group1 and 2 patients in group 2.

According to Jaswant Goyal *et al.* [2], a low dose Telmisartan–Amlodipine combination has demonstrated significantly greater BP reductions for both SBP and DBP compared to high-dose monotherapy of Telmisartan and Amlodipine.

According to Suresh V Sagarad *et al.* [13], the telmisartan and chlorthalidone combination was effective in the patients who remained uncontrolled after being on telmisartan and HCTZ combination in a similar dosage.

Hisatoshi Bekki *et al.* [14], suggest that combination therapy with telmisartan with amlodipine may be more beneficial than valsartan or candesartan plus amlodipine treatment for controlling brachial and central BP, which could lead to more favorable cardiovascular outcomes with these drug combinations.

CONCLUSION

Hypertension is one of the major public health challenges worldwide. The safety and efficacy of combination therapy of Telmisartan with Amlodipine and Telmisartan with Chlorthalidone were assessed. The combination of telmisartan plus amlodipine is equally effective as the combination of telmisartan plus chlorthalidone in decreasing SBP, DBP, HR, and MAP. There was no significant difference between the two treatment groups on serum electrolyte levels (Na, Ca, K, Mg, Cl). No major adverse drug reactions were noted during the study period. Further studies with larger sample sizes and for a longer duration are necessary to confirm the above results.

LIMITATIONS OF THE STUDY

It is an open-labeled prospective study and hence results cannot be generalized to the entire population. The sample size is 120; had the sample size been big, the results would have been more accurate and a long-term follow-up for one year will show the long-term benefits and side effects of the drug.

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AUTHORS CONTRIBUTIONS

All authors have made significant contributions to writing the manuscript, reviewing and editing, and submission.

CONFLICTS OF INTERESTS

Declared none

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