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A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF FIXED DOSE COMBINATION OF TELMISARTAN WITH HYDROCHLOROTHIAZIDE VERSUS TELMISARTAN WITH CHLORTHALIDONE IN ESSENTIAL HYPERTENSION AT A TERTIARY CARE HOSPITAL

Pharmaceutical Science

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ABSTRACT

Background: Hypertension is a common public-health challenge presents as a tip of iceberg, particularly past middle age. It is not a disease in itself, but is an important risk factor for coronary heart disease, stroke, renal disease and other vascular complications leading to cardiovascular mortality and morbidity worldwide. **Methods:** 100 hypertensives who have not achieved target BP (<140/90 mm Hg – JNC 8) with Telmisartan 40 mg/day tablet for four weeks were assigned into two groups of 50 each and randomized in a 1:1 ratio using computer random sequence generator (www.randomization.com) to receive either FDC of Telmisartan 40 mg + HCTZ 12.5 mg or Telmisartan 40 mg + CTD 6.25 mg tablet once daily in the morning. Efficacy was measured by reduction in blood pressure and at week 4, 8 and 12 from baseline. Safety was assessed by monitoring treatment emergent adverse effects. Data analysed by using repeated measure ANOVA, unpaired and paired't' test for continuous data and chi-square test for categorical data. **Results:** Telmisartan + CTD significantly reduced the DBP at 8 and 12 weeks compared to Telmisartan + HCTZ. A greater proportion of patients treated with Telmisartan + CTD achieved the target BP as compared to those patients who were treated with Telmisartan + HCTZ. Telmisartan + HCTZ and Telmisartan + CTD both reduced pulse rate significantly (p value < 0.001). There was no statistically significant difference in the reduction of pulse rate at the end of 12 weeks between the groups although numerically the reduction was less in the Telmisartan + CTD group. **Conclusion:** Telmisartan + CTD was found to be an effective and safe combination therapy in patients who failed monotherapy with Telmisartan in stage I hypertension compared to Telmisartan + HCTZ combination.

KEYWORDS

Hypertension ; Telmisartan ; Hydrochlorthiazide ; Chlorthalidone

INTRODUCTION

Hypertension is a progressive cardiovascular syndrome arising from interrelated aetiologies.[1] It is an important modifiable risk factor for cardiovascular, cerebrovascular, renal mortality and morbidity. On an average, it affects 25-30% of adult population in India which is the seventh highest contributor to premature death. In 2005, 26% of hypertensive patients were estimated worldwide which is projected to be 60% by 2025.[2] At 40-69 years of age, an increment of 20 mmHg in systolic BP or 10 mmHg in diastolic BP estimates to double this risk.[3]

Anti-hypertensive medications reduce cardiovascular deaths by decreasing incidence of stroke, myocardial infarction and heart failure by 35-40%, 20-25% and 50% respectively. Hence, meticulous control of hypertension is essential.[4]

Use of fixed-dose combinations have advantages in improving efficacy, patient-perceived wellness, cost, convenience, adherence and side effects.[5] One such combination is that of an angiotensin receptor blocker with a diuretic.

Telmisartan is an ARB has unique pharmacological properties like longer half-life, highly lipophilic that facilitates oral absorption, large volume of distribution, cardioprotective effects and PPAR-gamma inducing property suggests that it exerts anti-inflammatory, anti-oxidative property, improves insulin sensitivity, anti-proliferative effects on vascular walls and reduces triglyceride levels contributing to lower atherosclerotic risk.[6]

Hydrochlorothiazide is a thiazide diuretic used for more than 60 years has direct vasodilator effect, carbonic anhydrase inhibiting property, high incidence of electrolyte changes and metabolic abnormalities.[7]

In contrast to HCTZ, Chlorthalidone is 1.5-2 times more potent and efficacious with longer duration of action, high volume of distribution, good efficacy-to-side effect ratio with respect to hypokalaemia, lowers SBP, has pleiotropic effects, improves lipid profile, reduces high uric acid levels, cardiovascular events and left ventricular mass over time in hypertension.[7]

Addition of thiazide diuretics exerts an additive BP reduction because of their different but complementary mechanism of action, counteracting the increase in sodium and water retention and effect on PVR produced by other antihypertensive medications. Hence, a preferred combination is a low-dose thiazide with a RAAS inhibitor (ACE-I, ARB, Mineralocorticoid receptor antagonists or Aliskiren) due to its contribution for additive lowering of BP.[7]

Considering the paucity of comparative studies between Telmisartan with HCTZ and Telmisartan with CTD in essential hypertension with regard to efficacy and safety amongst Indian patients, this study was undertaken.

MATERIALS & METHODS

This study is a Randomized, , Open label, Prospective, Comparative Study conducted at Department of Medicine at Victoria hospital attached to Bangalore Medical College and Research Institute, Bengaluru. The protocol was approved with the Ethics Committee of our Institute and adhered to the tenets of the Declaration of Helsinki.

Patients with essential hypertension attending the diabetic clinic Out-Patient department aged between 18 and 60 years belonging to either gender between November 2018 to May 2020 were included after obtaining written informed consent.

Statistical Analysis

The Continuous data in this study will be assessed using repeated measure ANOVA and un paired 't' test. Categorical data will be assessed using chi-square test.

Data was collected and continuous variables were expressed as Mean ± Standard Deviation (parametric data) or as median and inter quartile range (non-parametric data). The continuous data in this study was analysed using repeated measure ANOVA (analysis of variance) for intragroup comparison and unpaired 't' test (parametric data) for intergroup comparison. Non-parametric continuous variables were analysed using Mann Whitney 'U' test for intergroup comparison. Categorical data was expressed as percentages/proportions and was analysed using chi-square test. $p < 0.05$ was considered statistically significant. Statistical analysis was performed using Vassar Stats software

RESULTS

115 patients were screened for the study of whom 100 patients who met the inclusion and exclusion criteria and gave written informed consent to participate were enrolled in the study. The flow chart of recruitment, randomization and follow up is depicted in figure 1. Group 1 received

Telmisartan 40 mg/day + HCTZ 12.5 mg/day, Group 2 received Telmisartan 40 mg/day + CTD 6.25 mg/day for 12 weeks.

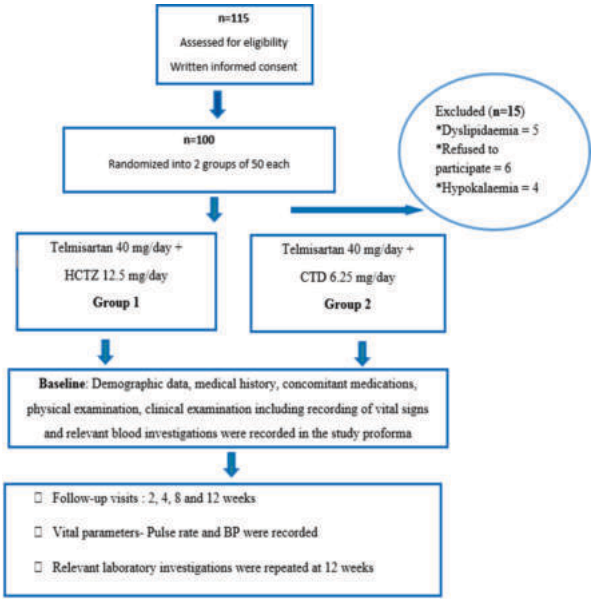


Figure 1: Flow Chart of Recruitment, Randomisation and Follow up

Demographic Characteristics

Table 1: Baseline Demographic Characteristics

Parameters	Group 1 Telmisartan 40 mg/day + HCTZ 12.5 mg/day (n=50)	Group 2 Telmisartan 40 mg/day + CTD 6.25 mg/day (n=50)	p value
Age (years) (Mean ± SD)	54.06 ± 4.41	54.52 ± 4.38	0.60*
Gender- n(%)			0.84**
Male	28 (56%)	30 (60%)	
Female	22 (44%)	20 (40%)	
Habits- n(%)			0.66**
Smoking	14 (28%)	17 (34%)	0.82**
Alcohol	12 (24%)	14 (28%)	
Co-morbidities n(%)			0.68**
DM	15 (30%)	12 (24%)	
CVA	03 (06%)	05 (10%)	
Hypothyroidism	02 (04%)	04 (08%)	
Ischemic heart disease	01 (02%)	01 (02%)	

* Data analysed using unpaired t test, **Data analysed using Chi-square, p<0.05 is considered statistically significant, DM=Type 2 diabetes mellitus, CVA=Cerebrovascular accidents

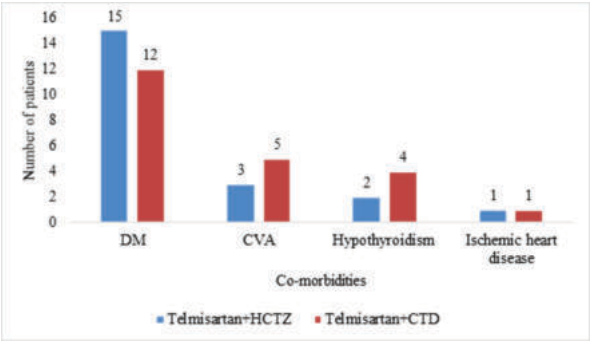
The mean age was 54.06 ± 4.41 years in the Telmisartan + Hydrochlorothiazide group and 54.52 ± 4.38 years in the Telmisartan + Chlorthalidone group (p value = 0.60).

Both the study groups were gender matched. There were 28 (56%) male and 22 (44%) female patients in the Telmisartan + HCTZ group and 30 (60%) male and 20 (40%) female patients in the Telmisartan + CTD group (p value = 0.84).

In the Telmisartan + HCTZ group, 14 (28%) were smokers and 12 (24%) alcoholics and in Telmisartan + CTD group, 17 (34%) smokers and 14 (28%) alcoholics.

CO-MORBIDITIES

In the Telmisartan + HCTZ group, 29 (58%) patients had no comorbid conditions. Out of the remaining 42%, 15 (30%) of them had Type 2 Diabetes Mellitus, 03 (06%) had Cerebrovascular accidents, 02 (04%) had Hypothyroidism and 01 (02%) had Ischemic heart disease. In the Telmisartan + CTD group, 28 (56%) patients had no comorbid conditions. Out of the remaining 44%, 12 (24%) of them had Type 2 Diabetes Mellitus, 05 (10%) had Cerebrovascular accidents, 04 (08%) had Hypothyroidism and 01 (02%) had Ischemic heart disease.



Graph 1: Comorbidities in Study Groups

a) Measurement of Reduction in Blood Pressure:

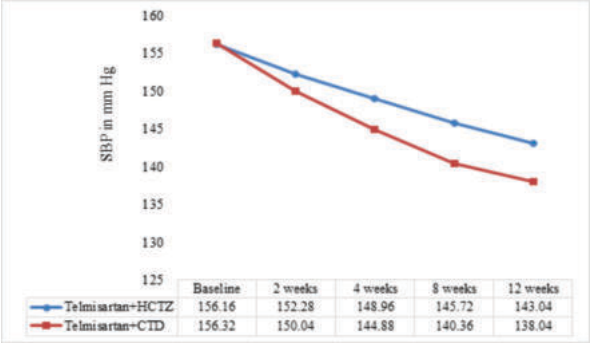
The baseline mean BP was comparable between the two groups (SBP: p value = 0.59, DBP: p value = 0.48). SBP/DBP was 156.16±1.45/ 95.56±2.26 mm Hg in the Telmisartan + HCTZ group and 156.32±1.58/ 95.88±2.34 mm Hg in the Telmisartan + CTD group.

Table 2 shows the mean BP in the Telmisartan + HCTZ and Telmisartan + CTD groups at baseline and at each of the follow up visits. The mean BP after 12 weeks of treatment was 143.04±5.05/ 86.24±6.28 mm Hg in the Telmisartan + HCTZ group and 138.04±6.41/ 83.24±6.35 mm Hg in the Telmisartan + CTD group. Telmisartan + HCTZ and Telmisartan + CTD effectively reduced BP compared to baseline (p value < 0.0001) at the end of 12 weeks. Graph 2, 3 represents the mean SBP and DBP in both the groups at baseline and at each follow up visits respectively.

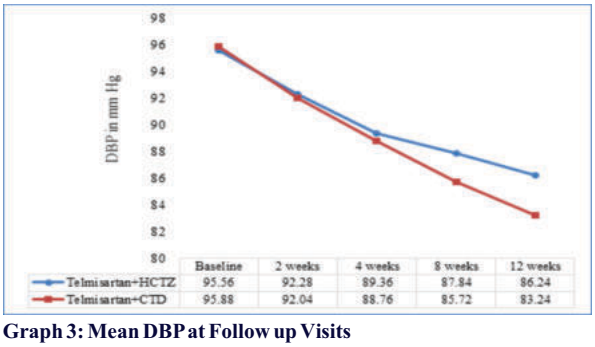
Table 2: Mean BP at Follow up Visits

Groups	Group 1 Telmisartan 40 mg/day + HCTZ 12.5 mg/day		Group 2 Telmisartan 40 mg/day + CTD 6.25 mg/day	
(Mean±SD) mm Hg	SBP	DBP	SBP	DBP
Baseline	156.16±1.45	95.56±2.26	156.32±1.58	95.88±2.34
2 weeks	152.28±4.31	92.28±3.26	150.04±4.15	92.04±3.37
4 weeks	148.96±4.95	89.36±3.56	144.88±5.03	88.76±3.59
8 weeks	145.72±4.97	87.84±4.42	140.36±6.28	85.72±4.92
12 weeks	143.04±5.05	86.24±6.28	138.04±6.41	83.24±6.35
p value	<0.0001*†	<0.0001*†	<0.0001*†	<0.0001*†

*Data analysed by repeated measures ANOVA (intra-group comparison), † p value < 0.05 is considered statistically significant



Graph 2: Mean SBP at Follow up Visits

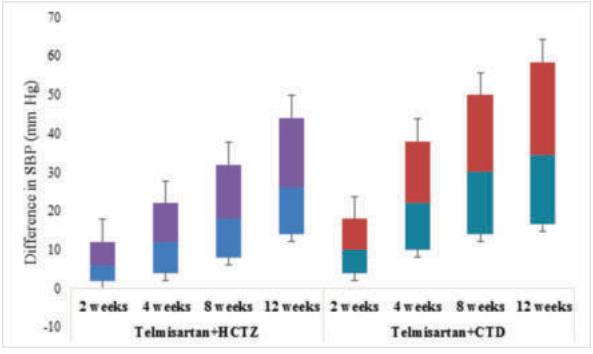


Graph 3: Mean DBP at Follow up Visits

Table 3: Comparison of Difference in SBP Values at Each Visit from Baseline

	SBP		
	Group 1 Telmisartan + HCTZ	Group 2 Telmisartan + CTD	p value
2 weeks			
Median	4	6	0.0011*†
IQR	6-2	8-4	
4 weeks			
Median	8	12	0.0001*†
IQR	-2-6	10-2.5	
8 weeks			
Median	10	16	0.0001*†
IQR	-2-14	19.5-6	
12 weeks			
Median	12	18	0.0001*†
IQR	18-10	24-12.5	

*Data analysed by Mann Whitney U test (intergroup comparison), , p value <0.05 is considered statistically significant. IQR-Inter quartile range

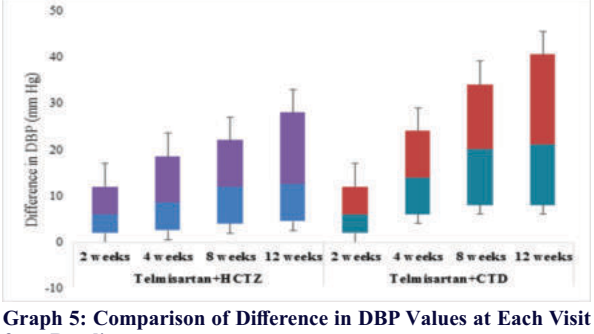


Graph 4: Comparison of Difference in SBP Values at Each Visit from Baseline

Table 4: Comparison of Difference in DBP Values at Each Visit from Baseline

DBP			
	Group 1 Telmisartan + HCTZ	Group 2 Telmisartan + CTD	p value
2 weeks			
Median	4	4	0.378*
IQR	6-2	6-2	
4 weeks			
Median	6	8	0.234*
IQR	10-2.5	10-6	
8 weeks			
Median	8	12	0.0101*†
IQR	10-4	14-6	
12 weeks			
Median	8	13	0.0128*†
IQR	15.5-4.5	19.5-6	

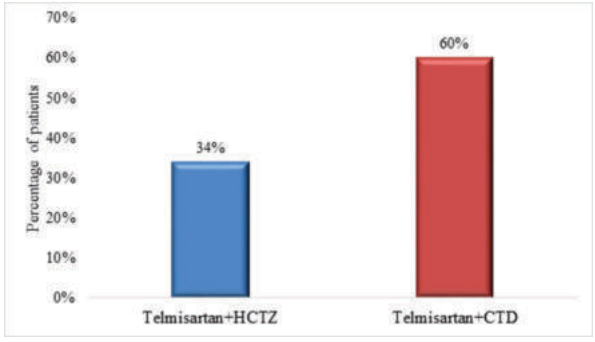
*Data analysed by Mann Whitney U test (intergroup comparison), † p value <0.05 is considered statistically significant. IQR-inter quartile range



Graph 5: Comparison of Difference in DBP Values at Each Visit from Baseline

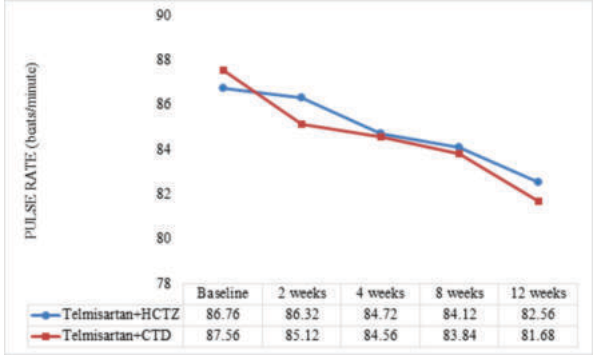
Target BP Achieved

30 (60%) patients in the Telmisartan + CTD group attained the target BP of <140/90 mm Hg compared to 17 (34%) patients in the Telmisartan + HCTZ group which was statistically significant (p value = 0.016) at the end of 12 weeks.



Graph 6: Percentage of Patients Achieving Target BP

The baseline mean PR was comparable between the two groups (p value = 0.63). It was 86.76±8.64 in the Telmisartan + HCTZ group and 87.56±7.93 beats per minute in the Telmisartan + CTD group. The mean PR after 12 weeks of treatment was 82.56±3.92 in the Telmisartan + HCTZ group and 81.68±4.13 beats per minute in the Telmisartan + CTD group. The pulse rate reduced in both the groups at the end of 12 weeks compared to the baseline (p value <0.0001). There was no significant difference in pulse rate between the groups at all the follow up visits (p value = 0.27). Graph 7 shows the mean PR in the Telmisartan + HCTZ and Telmisartan + CTD groups at baseline and at each of the follow up visits.

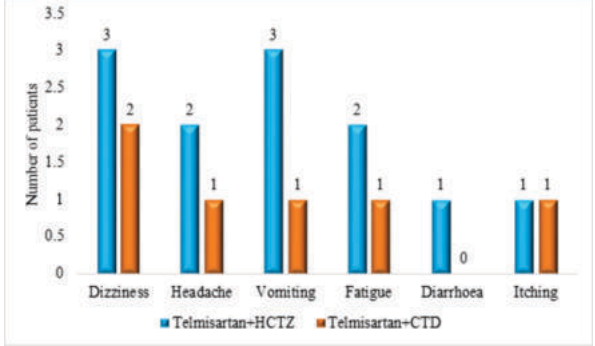


Graph 7: Mean PR at Follow up Visits

Evaluation of Safety Parameters

The adverse effects encountered were mild to moderate in nature and there was no statistically significant difference between the groups (p value = 0.06).

Graph 8 gives the various adverse effects encountered in both the groups.



Graph 8: Adverse Effects in Both the Groups

DISCUSSION

Hypertension is a common public-health challenge presents as a tip of iceberg, particularly past middle age. It is not a disease in itself, but is an important risk factor for coronary heart disease, stroke, renal

disease and other vascular complications leading to cardiovascular mortality and morbidity worldwide.[8,9,10] Thus, it is popularly known as the 'Silent killer' as it shows no early symptoms.[11] Systemic hypertension accounts for 69% of patients with a first myocardial infarction, 77% with a stroke, 74% with chronic heart failure and 60% with peripheral arterial disease.[12] Epidemiological studies have confirmed that higher the BP greater is the risk of cardiovascular disease.[8]

Expert opinion states that more than a quarter of the world's adult population, nearly 1 billion had hypertension in 2008 and this proportion will be increased to 1.56 billion by 2025, estimated to have overall prevalence of 27% globally. In India, the prevalence of hypertension is around 31.4% ranging from 13.6% to 47.9% in various studies.[13]

The mean age of our enrolled patients was 54.06 ± 4.41 years in the Telmisartan + HCTZ group and 54.52 ± 4.38 years in the Telmisartan + CTD group which was matched at baseline (p value = 0.60). Similar age representation was found in study done by Suresh V Sagarad et al with mean age of 54.88 ± 9.57 years.[14] Recent evidence in normotensives suggested that individuals who are at 55 years of age have a 90% lifetime risk for developing hypertension.[15]

A meta-analysis of 137 RCTs in 2010 proved the effectiveness of CTD and HCTZ as monotherapy for hypertension. A total of 29 trials of CTD and 108 trials of HCTZ were assessed based on dose and study duration of less than one year. A pooled analysis with CTD produced a statistically significant decrease in SBP when compared with HCTZ. The median change in SBP associated with the median dose of HCTZ was −17 mm Hg, compared to −26 mm Hg for CTD.[16] The above findings are congruent with our study, which showed the median change in SBP with Telmisartan + HCTZ group was −12 mm Hg compared to −18 mm Hg for Telmisartan + CTD group of patients at the end of 12 weeks (p value = 0.0001).

Patients with Telmisartan + HCTZ and Telmisartan + CTD group both reduced pulse rate significantly ($p < 0.001$). The pulse rate was reduced from 86.76 ± 8.64 to 82.56 ± 3.92 beats per minute in the Telmisartan + HCTZ group and from 87.56 ± 7.93 to 81.68 ±4.13 in the Telmisartan + CTD group. There was no statistically significant difference in the reduction of pulse rate at the end of 12 weeks between the groups although numerically the reduction was less in the Telmisartan + CTD group (p value = 0.27). In a review by Amrinder Singh et al, it was observed that after 6 months of treatment with Telmisartan alone reduced the heart rate from 78.0 to73.8 beats/minute.[17] In a previous study done by Asmar R et al on effect of Telmisartan 40 mg for 3 weeks in Type 2 diabetes patients with mild to-moderate hypertension reduced arterial stiffness measured by pulse wave velocity. Arterial stiffness is an important risk factor for cardiovascular mortality, hence improvement in arterial stiffness and endothelial dysfunction may offset deleterious hemodynamic effects. This may translate clinically into greater reductions in cardiovascular morbidity and mortality.[6]

CONCLUSION

At 12 weeks, both combinations of Telmisartan + Hydrochlorothiazide (HCTZ) and Telmisartan + Chlorthalidone (CTD) significantly reduced systolic and diastolic blood pressure ($p < 0.0001$). The CTD combination achieved greater SBP reduction at 2, 4, 8 and 12 weeks and greater DBP reduction at 8 and 12 weeks compared to HCTZ. More patients on Telmisartan + CTD reached target BP. Both therapies significantly lowered pulse rate ($p < 0.001$) but had no significant inter-group difference at week 12. They were well tolerated with no serious adverse metabolic or safety concerns, supporting Telmisartan + CTD as an effective and safe option for stage-I hypertensives unresponsive to monotherapy.

Conflict of Interest : None

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