

# The Antihypertensive Efficacy of Chlorthalidone and Telmisartan in Indian Hypertensive Patients who were Uncontrolled with Hydrochlorothiazide and Telmisartan Combination-A Prospective and an Open Label Study

SURESH V SAGARAD, SUDHA BIRADAR KERURE, CHAITANYA KUMAR S, RAMAKRISHNA MR

## ABSTRACT

**Objective:** The primary objective of this study was to evaluate the antihypertensive efficacy of the chlorthalidone and telmisartan combination in Indian hypertensive patients who remained uncontrolled after taking the hydrochlorothiazide and telmisartan combination.

**Methods:** A total of 100 eligible patients were enrolled in this prospective, open label study. The patients were given telmisartan (40 mg) and chlorthalidone (12.5 mg), who had not achieved the target blood pressure (140/90 mmHg) despite taking the combination of telmisartan (40 mg) and hydrochlorothiazide (12.5 mg). The assessment was done at the end of 4 weeks and 8 weeks.

**Results:** The mean SBP and DBP after taking telmisartan (40 mg) and hydrochlorothiazide (12.5 mg) were 154.88±9.57 (range 144 to 160) mmHg and 99.37±2.78 (range 92 to 106).

At the end of 4 weeks of being on telmisartan (40 mg) and chlorthalidone (12.5 mg), the mean SBP and DBP were 145.56±5.12 (range 134 to 158) mmHg and 95.14±4.27 (range 84 to 100) mmHg. Significant falls in the SBP (5.32±2.64) and DBP (4.18±2.48) were noted at the end of the 4 week therapy. They were sustained at the end of 8 weeks also. The SBP target (<140 mmHg) was achieved in 24 % patients. The DBP target (<90 mmHg) was achieved in 19% patients. The combined SBP and DBP target (<140/90 mmHg) was achieved in 15% patients. No significant clinical adverse events were reported. Similar falls in the SBP and DBP were noted in the subgroups (smokers, females, diabetics, etc).

**Conclusions:** The hypertensive patients who do not achieve the target blood pressures on telmisartan and hydrochlorothiazide can be switched on to the telmisartan and chlorthalidone combination. This combination is effective and well tolerated.

**Key Words:** Chlorthalidone, Hydrochlorothiazide, Telmisartan, Hypertension

## INTRODUCTION

Hypertension is a major risk factor for all cardiovascular events. Of a number of risk factors that are directly responsible for an increase in the cardiovascular morbidity and mortality, high blood pressure (BP) is one of the most important and independent risk factors which affects 24-36% of the adult population in the developed countries [1]. Epidemiologic studies have established a strong and linear relationship between BP and cardiovascular disease and randomized trials have documented that the BP reductions which are achieved by the antihypertensive drugs confer a cardiovascular protection [2]. Among the antihypertensive drugs, the thiazide type diuretics confer a significant reduction in cardiovascular events [3-9]. Their strong record of evidence, low costs and tolerability have made the low dose thiazide like diuretics the initial therapy in most of the anti hypertensive regimens [10]. However, many of the pivotal studies have used chlorthalidone as the initial therapy, believing that it has a longer duration of action. A longer duration of action provides a night time blood pressure control and hence, it is effective in providing additional protection from stroke and myocardial infarction, which was

shown by Earnst et al., [11,12]. In a recent retrospective cohort study, Lund and Ernst examined the effectiveness of chlorthalidone and hydrochlorothiazide (HCTZ) among the new thiazide users. Their study provided real world clinical data which supported the potential efficacy advantage of chlorthalidone among the patients who tolerated the drug and remained persistent with the treatment [13].

A majority of the hypertensive patients cannot be controlled by using one drug. JNC 7, as well as the European Society of Hypertension and Cardiology and the German Hypertension League, have stated that a large proportion of hypertensive patients will require a combination of two or more antihypertensive agents to achieve the desired target BP [10,14,15].

Chlorthalidone has been studied in Indian patients. It has been used in combination with metoprolol XL, losartan and atenolol [16-18]. Pareek et al., have reported that chlorthalidone, in combination with metoprolol XL, is as effective and well tolerated as the widely used combination of metoprolol XL and HCTZ. However, there is no report on the use of telmisartan in combination with

chlorthalidone in Indian hypertensive patients. This study intended at evaluating the efficacy of this combination in those patients who could not reach the target with the widely used combination of telmisartan and HCTZ.

## MATERIALS AND METHODS

This prospective, open label study was conducted at Navodaya Medical College, Raichur, in the northern Karnataka part of India, during the period from January 2011 to April 2012. Hypertensive male and female patients who were aged >18 years, who attended the out-patients clinics of the investigators, were evaluated for inclusion in the study. Uncontrolled BP was defined as >140 mm Hg systolic and / or > 90 mmHg diastolic despite being on telmisartan 40 mg and HCTZ 12.5 mg for more than 4 weeks and despite having a good tolerance and compliance. The patients with pre existing severe co-morbidities (renal failure, serum creatinine >2mg/dl, hepatic failure, SGOT / SGPT->3 times of the upper level of the normal, known malignancies, a recent acute illness, a recent major surgery, etc) were excluded from the study. Those with an SBP of >160 and a DBP of >110 were also excluded. The patients were shifted to the telmisartan 40 mg and chlorthalidone 12.5 mg daily combination. The efficacy of the therapy was evaluated by the BP measurements at 4 weeks and 8 weeks. The BP was measured by the auscultatory method. The measurements were performed after 10 minutes of rest in duplicate, which were separated by 2 minutes and then, the average of the measurements was taken. If the first two readings differed by more than 5 mmHg, an additional reading was obtained and the average of the two closest readings was taken. The patients were termed as responders if the BP was <140/90 mmHg. The safety evaluation was based on the adverse events which were reported. The patients who received drugs other than the study drugs for the associated illnesses were continued on them as per the discretion of the treating physician. However, care was taken not to alter the dosage of the drugs which affected the BP (like beta blockers for angina).

This study was conducted according to the Good Clinical Practice guidelines and the Declaration of Helsinki, and the protocol was approved by the ethics committee of the hospital. Written informed consents were obtained from all the patients prior to their inclusion into the study.

## STATISTICAL ANALYSIS

The primary objective behind the assessment of the efficacy was to compare the mean falls in the SBP and the DBP after 4 and 8 weeks of the treatment change. The basic descriptive statistics were calculated and expressed as mean  $\pm$  SD. The data at baseline and at 4 weeks and 8 weeks were compared by using t tests with a level of significance of 0.05. The statistical analysis was performed by using the software, Minitab 16.

## RESULTS

During the study period [Table/Fig-1], totally one hundred (60 males and 40 females) patients were enrolled. A majority were middle aged people (54.88 $\pm$ 9.57 years, range 38 to 72). Diabetes was present in 30 patients. Known coronary artery disease was present in 20 patients. Thirty patients had been receiving medications for more than five years, 30 patients had been receiving them for more than one year and 40 patients had been receiving them for less than one year. Current smoking was noted in 30 patients. The SBP and the DBP were 150.88 $\pm$ 3.68 mmHg and 99.32 $\pm$ 2.78 mmHg at

the baseline. At 4 weeks [Table/Fig-2], the SBP and the DBP were 145.56 $\pm$ 5.12 and 95.14 $\pm$ 4.27 mmHg.

There were significant falls in the SBP (5.32 $\pm$ 2.64 mmHg, P <0.05) and the DBP (4.18 $\pm$ 2.48 mmHg, P <0.05) at the end of 4 weeks as compared to those at the baseline. This trend was sustained even at 8 weeks. No further significant falls in the SBP or the DBP were noted after 4 weeks (5.32 $\pm$ 2.64 and 4.18 $\pm$ 2.48 mmHg at 4 weeks vs 5.30 $\pm$ 2.58 and 4.0 $\pm$ 2.33 mmHg at 8 weeks P=NS). The SBP target (<140 mmHg) was achieved in 24 patients (24%). The DBP target (<90 mmHg) was achieved in 19 patients (19%). The combined SBP and DBP target (<140/90 mmHg) was achieved in 15 patients (15%).

A similar fall in the SBP was observed in the subgroups which were analyzed, like males vs females (5.40 $\pm$ 2.88 vs 5.22 $\pm$ 2.55 mmHg P=NS), smokers vs non smokers (5.44 $\pm$ 2.66 vs 5.38 $\pm$ 2.78 mmHg P=NS) and diabetics vs non diabetics (5.51 $\pm$ 2.55 vs 5.44 $\pm$ 2.61 mmHg P=NS). Similar results were also observed in the DBP fall among the subgroups, like males vs females (4.12 $\pm$ 2.44 vs 4.22 $\pm$ 2.48 mmHg, P=NS), smokers vs non smokers (4.22 $\pm$ 2.38 vs 4.33 $\pm$ 2.36 mmHg P=NS) and diabetics vs non diabetics (4.44 $\pm$ 2.38 vs 4.34 $\pm$ 2.38 mmHg, P=NS). No difference in the BP response was noted with the previous durations of the medications i.e., less than one year vs 1 to 5 years vs more than 5 years (SBP 5.31 $\pm$ 2.63 vs 5.33 $\pm$ 2.53 vs 5.29 $\pm$ 2.50 P=NS, DBP 4.20 $\pm$ 2.46 vs 4.22 $\pm$ 2.38 vs 4.19 $\pm$ 2.41 P=NS). No clinically significant adverse events were reported during the study period.

## DISCUSSION

Hypertension is one of the most important preventable causes of the premature morbidity and mortality worldwide and its management is one of the most common interventions in the primary care. Epidemiological and randomized controlled trials have documented that the BP reduction which is achieved by the anti hypertensive drugs confer a cardiovascular protection [2]. Life style modifications and pharmacotherapy are the cornerstones in the BP reduction. Various guidelines are available, for choosing a pharmacological agent [10,19,20]. The pharmacological agent and the dosage are decided on the basis of the baseline BP and co-morbid illness.

A large number of drugs are currently available for reducing the BP. More than two-thirds of the hypertensive individuals cannot be controlled by using one drug and they will require two or more anti-hypertensive agents which can be selected from the different drug classes. In the ALLHAT trial, 60% of those whose BPs were controlled to <140/90 mmHg received two or more agents, and only 30% overall, were controlled by using one drug [3]. In hypertensive patients with lower BP goals or with substantially elevated BPs, three or more anti-hypertensive drugs may be required. In JNC 7 which was published soon after the ALLHAT trial, the thi-

Age (mean $\pm$ SD) yrs	54.88 $\pm$ 9.57
M:F	60:40
Diabetes (N, %)	30 (30%)
CAD (N, %)	20 (20%)
Current smoking (N,%)	30 (30%)
SBP (mean $\pm$ SD) mmHG	150.88 $\pm$ 3.68
DBP (mean $\pm$ SD) mmHg	99.32 $\pm$ 2.78

**[Table/Fig-1]:** Baseline characteristics

SBP (Baseline vs 4 weeks, all patients)	150.88±3.68 vs 145.56±2.64	P <0.05
DBP (Baseline vs 4 weeks, all patients)	99.32±2.78 vs 95.14±4.27	P <0.05
SBP fall in Male vs Female at 4 weeks	5.40±2.88 vs 5.22±2.55	P = NS
SBP fall in Smokers vs Non-Smokers at 4 weeks	5.44±2.66 vs 5.38±2.78	P = NS
SBP fall in Diabetes vs Non-Diabetes at 4 weeks	5.51±2.55 vs 5.44±2.61	P = NS
DBP fall in Male vs Female at 4 weeks	4.12±2.44 vs 4.22±2.48	P = NS
DBP fall in Smokers vs Non-Smokers at 4 weeks	4.22±2.38 vs 4.33±2.36	P = NS
DBP fall in Diabetes vs Non-Diabetes at 4 weeks	4.44±2.38 vs 4.34±2.38	P = NS

**[Table/Fig-2]:** Comparison at 4 weeks (mean ± SD, mmHg)

azide type diuretics were recommended as the first line drugs in the absence of any compelling indications. Further, it stated that when the BP was >20 mmHg above the systolic goal or >10 mm Hg above the diastolic goal, consideration should be given to initiate the therapy with two drugs, either as separate prescriptions or in fixed dose combinations [10]. Our patients who were enrolled were on two drug fixed dose combinations i.e., telmisartan 40 mg and HCTZ 12.5 mg. However, they had not achieved the target BP and hence, they required either an escalation of the dosage or the addition of another anti-hypertensive agent from a different class. The Telmisartan and HCTZ combination has been in the Indian market for quite some time and it has been a widely accepted combination after the ONTARGET results - telmisartan was equivalent to ramipril in the patients with vascular diseases or high risk diabetes and it was associated with less angioedema and cough [21]. A majority of our enrolled patients had compelling indications for them to use an ARB like telmisartan (diabetes, CAD). Also, based on the recent NICE recommendations, telmisartan can be the first line agent in patients who are aged <55 years (the mean age was 54.88±9.57 years in this study) [19]. Further, the NICE guidelines do suggest the use of a thiazide like diuretic such as chlorthalidone (12.5 to 25 mg once daily) or indapamide (a 1.5 mg modified release once daily or 2.5 mg once daily) if the treatment with a diuretic is being started, or changed. Recently, in India, chlorthalidone is available for monotherapy as well as in various fixed dose combinations (with telmisartan, olmesartan, metoprolol XL and atenolol). Pareek et al., have reported the efficacy and safety of low dose chlorthalidone with losartan, metoprolol XL and atenolol [16-18]. However, there is no study which has evaluated the efficacy of the combination of chlorthalidone with telmisartan at present, though this combination is used frequently.

Our study has confirmed the findings of the earlier trials. The patients who are on HCTZ can be shifted to a similar dose of chlorthalidone safely and this is efficacious. In the current study, there were significant falls in the SBP and the DBP at the end of 4 weeks as compared to those at the baseline. This trend was sustained even at 8 weeks. The SBP target (<140 mmHg) was achieved in 24% patients, and the DBP target (<90 mmHg) was achieved in 19% patients. The combined SBP and DBP target (<140/90 mmHg) was achieved in 15% patients. A similar response which was seen in the subgroups which were analyzed was also encouraging.

We excluded the patients with a BP of 160/110 mmHg, as these patients would require a dose escalation and the addition of another drug from a different class as per the previous reports. No clinically significant adverse events were reported during the study period. This was expected as the enrolled patients had

tolerated the previous medications and as chlorthalidone was well tolerated in the doses which were used in this trial.

Our trial report supported the recommendation that chlorthalidone should be preferred if a thiazide like diuretic was considered in the anti-hypertensive therapy, as it was more potent and longer acting than the conventionally used HCTZ and had a stronger evidence base also [19,12,22 -24].

**Limitations:** This study has similar limitations as that of any open label trials. Ideally, a double blind randomized controlled trial is needed to confirm the results. Ambulatory BP monitoring is a better modality which can be used to assess the 24 hour BP reduction effects of the antihypertensives, which was not done in current study. The impact of the lifestyle changes after the enrollment was also not assessed.

## CONCLUSIONS

The results of this study demonstrated that the telmisartan and chlorthalidone combination was effective in the patients who remained uncontrolled after being on the telmisartan and HCTZ combination in a similar dosage. A significant proportion of patients can achieve the target BP without having to face any clinically significant adverse events. This combination can be tried before the dose escalation or before the addition of a third anti hypertensive agent.

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**AUTHOR(S):**

1. Dr. Suresh V Sagarad
2. Dr. Sudha Biradar Kerure
3. Dr. Chaitanya Kumar S
4. Dr. Ramakrishna MR

**PARTICULARS OF CONTRIBUTORS:**

1. Associate Professor, Department of Medicine, Navodaya Medical College & Hospital, Raichur, India.
2. Associate Professor, Department of OBG, Navodaya Medical College & Hospital, Raichur, India.
3. Associate Professor, Department of Medicine, Navodaya Medical College & Hospital, Raichur, India.
4. Associate Professor, Department of Medicine, Navodaya Medical College & Hospital, Raichur, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**

Dr. Suresh V Sagarad,  
Associate Professor, Department of Medicine,  
Navodaya Medical College, Raichur,  
Pin-584103, Karnataka, India.  
Phone: +919448139339  
E-Mail: drssagarad@hotmail.com

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