

# Triple drug combination of telmisartan, amlodipine and hydrochlorothiazide in the treatment of essential hypertension

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## ABSTRACT

**Background:** Triple drug therapy comprising angiotensin receptor blocker (ARB), calcium channel blocker (CCB) and hydrochlorothiazide (HCT) effectively controls essential hypertension as evident from the literature. This study was undertaken to assess the efficacy and safety of triple combination compared to the dual drug therapy. **Methodologies:** A total of 220 male and female patients with essential hypertension were enrolled in the study. The patients were divided into two groups. Group A received a bilayer tablet of FDC of Telmisartan + Amlodipine + HCT and group B received FDC tablet of Telmisartan + HCT. Both the treatments were administered once daily for twelve weeks. The patients were asked to follow-up on week 1, 2, 4, 6, 8 and 10 for periodic efficacy and safety evaluations. Effect on systolic blood pressure (SBP), diastolic blood pressure (DBP) and quality of life (QOL) were recorded during the course of the trial. **Results:** Blood pressure reduction (BP) to the desired goals was observed with both the treatments. The SBP and DBP reductions were superior in triple combination therapy than double combination. Both treatments improved QOL of patients. **Conclusion:** Triple drug combination of telmisartan, amlodipine and HCT may serve a potential role in achieving desired BP goals, in patients with essential hypertension, which are otherwise poorly managed by either monotherapy or dual drug therapy.

**Keywords:** Essential Hypertension; Telmisartan;

Amlodipine and HCT

## 1. INTRODUCTION

Treatment of essential hypertension has largely evolved from single drug therapy to combinations of drugs exhibiting different mechanisms of action. The prime objective for such experiments is to reduce BP effectively, as it reduces mortality and morbidity associated with stroke and coronary heart disease. Especially in patients with concomitant risk factors like diabetes, optimum values for BP is the need of the hour. In spite of many therapy advancements, effective BP control is far away from reality in many patients. A report says that only 37% of hypertensive patients in the US achieve the conservative goal of <140/90 mmHg of BP [1]. Multi drug combinations are the possible answers for the treatment of such difficult to control BP patients [2]. Many combinations have been tried in clinical trials and few are available worldwide. ARBs like losartan, olmesartan and telmisartan, were evaluated in combination with either HCT or CCB for their use in essential hypertension. Most of the clinical evidences showed superior efficacy of such combinations over monotherapies, with modest adverse events being reported [3,4] ARB-HCT combinations are getting increasingly popular in the antihypertensive therapy and prescriptions are continuing to be switched to these combinations. In recent times, more than two drugs were also combined for better clinical outcomes. ARB-CCB-HCT fixed dose combinations were also developed on the same lines. Olmesartan-amlodipine-HCT has been studied in randomized clinical trials for its efficacy &

safety and it has been concluded that this triple combination is superior in BP reduction, compared to dual combinations and it also showed comparable tolerability. [5,6].

The present study was undertaken to determine the BP lowering effect of telmisartan when combined with amlodipine and HCT compared to dual combination of telmisartan and amlodipine.

Telmisartan exerts its BP lowering effect by blocking angiotensin II receptors. In addition, telmisartan also has PPAR-gamma (Peroxisome Proliferator Activator Receptor) agonistic activity; this could be a potential reason for the better clinical outcomes with this molecule compared to other ARBs. Apart from effective BP lowering, telmisartan is also associated with renal protection, improved ventricular remodelling, reduced inflammation and oxidative stress, etc. [7-10]. Many authors have demonstrated the superiority of telmisartan when combined with other antihypertensives like amlodipine or HCT compared to monotherapy. [11-14]. Telmisartan combinations were also better in BP reduction compared to other ARB combinations [15]. Amlodipine is one of the most commonly used CCBs in the management of patients with hypertension. Amlodipine also exhibits plaque stabilisation properties and may prevent more number of events of stroke and myocardial infarction (MI) as compared to ARB [16,17]. HCT is a thiazide diuretic which helps to reduce BP by volume depletion. It has a long history of usage and has been tried in combination with many other antihypertensive drugs.

## 2. MATERIALS AND METHODS

This randomized, single blind study was conducted in accordance with ICH guidelines and declaration of Helsinki. A total of 220 male and female patients with essential hypertension were enrolled in the study, as per the inclusion/exclusion criteria defined in the protocol. All the patients were screened for their laboratory parameters, vital organ functions and BP (both sitting and supine) prior to enrolment. Patients with SBP 140 - 200 mmHg and DBP 90 - 120 mmHg were considered for the study. The patients were divided into two groups. Group A received a bilayer tablet of FDC of Telmisartan (40 mg) + Amlodipine (5 mg) + HCT (12.5 mg) and group B received FDC tablet of Telmisartan (40 mg) + HCT (12.5 mg). Both the treatments were administered once daily for twelve weeks. The patients were asked to follow-up on week 1, 2, 4, 6, 8 and 10 for periodic efficacy and safety evaluations. Effect on both SBP and DBP was recorded during the course of the trial. Both the therapies were also evaluated on the basis of Quality of Life (QOL) questioner and safety parameters. QOL was assessed by using a questionnaire based on the common problems

associated with elevated BP. The p values for evaluation parameters were calculated using single factor ANOVA.

## 3. RESULTS

The baseline parameters for both the groups were not statistically different. Total number of 208 patients completed the study with 12 patients considered as dropouts as they lost to follow up. A total number of 106 patients from group A and 102 patients of group B were taken for final analysis. The vital signs like body temperature, pulse rate and respiratory rate remained unchanged throughout the follow up visits in both the groups.

### 3.1. The Effect of Triple Drug Combination on Systolic Blood Pressure (SBP)

SBP measured at sitting and supine postures dropped considerably with both the treatments. Mean sitting SBP decreased from  $166.84 \pm 13.52$  mmHg at baseline to  $123.05 \pm 7.83$  mmHg at the end of week 12 in group A and from  $168.89 \pm 15.96$  mmHg at baseline to  $130.93 \pm 14.84$  mmHg at the end of week 12 in group B (**Table 1**). Similar results were seen in SBP measurements at supine posture (**Table 2**). The SBP drop from baseline is superior in triple combination compared to dual combination. However both the treatments showed statistically significant reduction in SBP from baseline values ( $p < 0.05$  calculated using one way ANOVA).

### 3.2. The Effect of Triple Drug Combination on Diastolic Blood Pressure (DBP)

Both the treatments showed statistically significant reduction in DBP compared to baseline values ( $p < 0.05$  calculated using one way ANOVA). Mean sitting DBP was decreased from  $103.62 \pm 13.05$  mmHg at baseline to  $81.17 \pm 8.62$  mmHg at the end of week 12 in group A. Similarly in group B, mean sitting DBP decreased from  $105.43 \pm 16.51$  mmHg at baseline to  $84.24 \pm 7.70$  mmHg at the end of week 12 (**Table 1**). Mean supine DBP also showed the similar trend which decreased from  $100.22 \pm 10.31$  mmHg to  $79.45 \pm 6.64$  mmHg in group A and from  $103.4 \pm 10.09$  mmHg to  $83.56 \pm 8.06$  mmHg in group B (**Table 2**).

### 3.3. Effect on Quality of Life (QOL)

The patients were asked questions based on the associated symptoms of essential hypertension, both before treatment and at the end of the treatment. The improvement was observed in symptoms such as light-headedness or faintness, sleepy feeling, weakness in limbs, blurring of vision, swelling in ankles at the end of the treatment period. Both the treatments were associated with improved QOL.

**Table 1.** SBP & DBP evaluation at sitting posture.

	Sitting			
	SBP		DBP	
	Group A	Group B	Group A	Group B
<b>Before Treatment (Mean ± SD)</b>	166.84 ± 13.52	168.89 ± 15.96	103.62 ± 13.05	105.43 ± 16.51
<b>After Treatment (Mean ± SD)</b>	123.05 ± 7.83	130.93 ± 14.84	81.17 ± 8.62	84.24 ± 7.70

**Table 2.** SBP & DBP evaluation at supine posture.

	Supine			
	SBP		DBP	
	Group A	Group B	Group A	Group B
<b>Before Treatment (Mean ± SD)</b>	165.75 ± 15.66	168.75 ± 16.50	100.22 ± 10.31	103.4 ± 10.09
<b>After Treatment (Mean ± SD)</b>	122.5 ± 9.38	129.42 ± 11.27	79.45 ± 6.64	83.56 ± 8.06

### 3.4. Investigators' Assessment of Therapy

Investigators' were asked to rate therapy as unsatisfactory, satisfactory, good and very good. According to investigators' rating more number of patients fell under the category of very good and good in group A compared to group B (Figure 1).

### 3.5. Patients' Assessment of Therapy

Figure 2 reveal the patients assessment of therapy based on similar ratings given above. More than 86% of patients in group A felt that the triple combination was either good or very good therapy.

### 3.6. Safety Evaluations

Both the treatments were tolerated well with few reports of adverse events. Nausea (3.77%), vomiting (4.72%), GI distress (3.77%) and tiredness (3.77%) were the major complaints from group A. Group B patients reported nausea (5.88%), vomiting (4.90%), headache (4.90%) and tiredness (6.86%) as the major problems. All the reported adverse events were of mild to moderate intensity and did not require any active management.

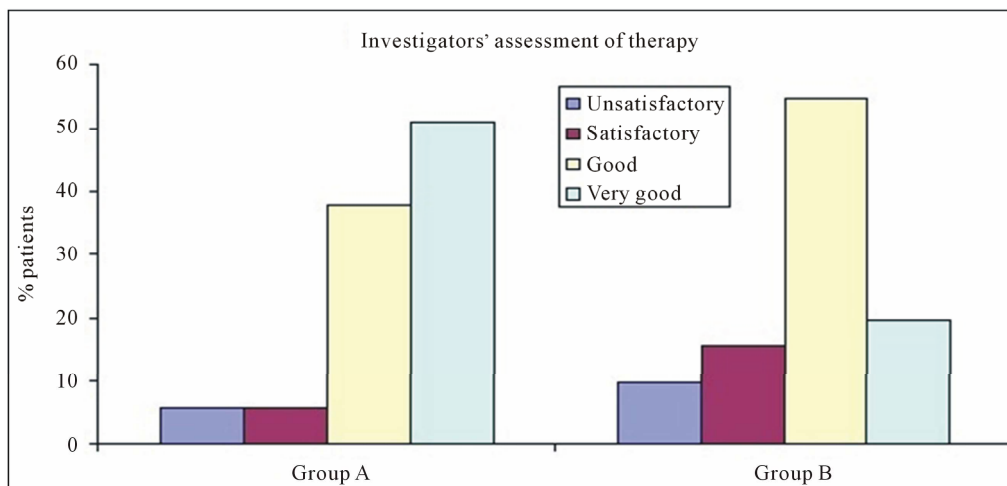
## 4. DISCUSSION

Intensive control of elevated blood pressure helps to prevent cardiovascular complications. Thus achieving BP goals is the major objective of the antihypertensive therapy. Monotherapy is often unsatisfactory for achieving desired BP control giving way for combinations of two or more drugs [18-20]. "Combination of the drugs having different mechanisms of action acts better in achieving BP goals" is the rationale for such combinations. The present study aimed to evaluate the effectiveness and

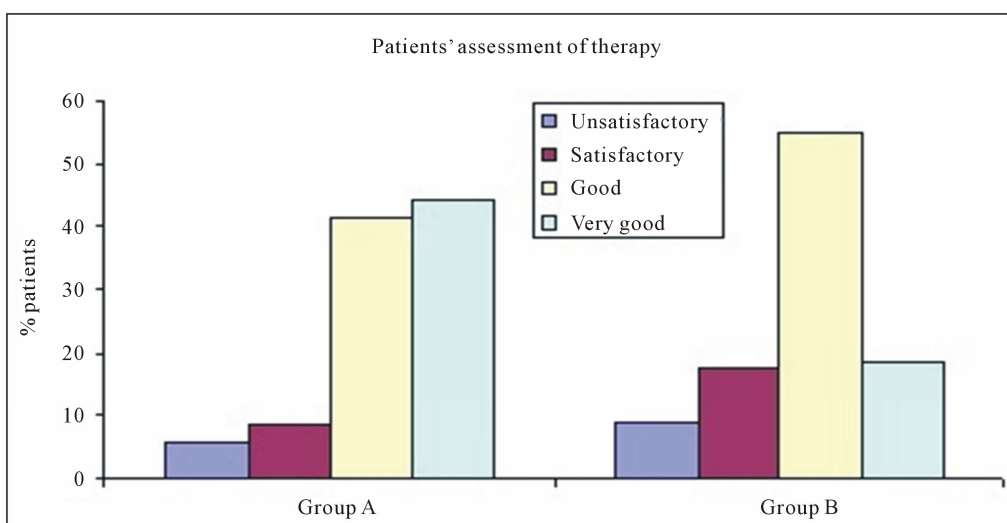
safety of triple combination of telmisartan with amlodipine and HCT. Similar combination with olmesartan is already in the therapeutics for essential hypertension. Telmisartan is superior to olmesartan, as evident from the scientific literature thus replacing olmesartan with telmisartan in triple drug combination may have beneficial effects [21,22].

The use of combination therapy in this study was consistent with the Seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high BP. It is also as per the European society of hypertension and European society of cardiology treatment guidelines. These guidelines recommend combination therapy in patients whose SBP is >20 mmHg above and DBP is >10 mmHg above the desired BP goals [23,24]. The availability of these drugs as a fixed dose combination in single tablet may offer additional advantage in terms of acceptance and compliance to the therapy.

The present study demonstrates the superiority of telmisartan, amlodipine and HCT triple combination over telmisartan and amlodipine combination. Both sitting and supine BP were monitored during the trial. The SBP reduced more efficiently in triple combination group than the dual combination group and the difference was statistically significant. DBP also showed similar trend in both the groups. Elevated BP hampers QOL as it is associated with many symptoms. QOL was improved in both the treatment groups as evident from the response to QOL questionnaire. The study medications were also evaluated on the basis of overall rating of therapy by investigators and also by patients. Both investigators and patients were of the opinion that triple combination of telmisartan, amlodipine and HCT is a better option than the treatment with telmisartan and amlodipine. Both the



**Figure 1.** Investigators' assessment of therapy.



**Figure 2.** Patients' assessment of therapy.

treatments were tolerated well and there was no evidence of significant increase in adverse events with the addition of extra drug in triple combination.

## 5. CONCLUSION

Telmisartan when combined with amlodipine and HCT showed better control of both SBP and DBP. Thus this combination may serve a potential role in achieving desired BP goals, in patients with essential hypertension, which are otherwise poorly managed by either monotherapy or dual drug therapy. At the same time studied triple drug combination exhibits comparable tolerability profile to that of dual drug combination.

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