

## Research Article

# Efficacy and safety of triple drug fixed-dose combination of telmisartan, amlodipine and hydrochlorothiazide in the management of hypertension

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### ABSTRACT

**Background:** High blood pressure (BP) is the most prevalent chronic disease in India and its prevalence is rapidly increasing among urban and rural populations. This study was conducted to assess the efficacy and safety of triple drug fixed dose combination of Telmisartan 40 mg, Amlodipine 5 mg and Hydrochlorothiazide 12.5mg.

**Methods:** 30 hypertensive patients having systolic blood pressure  $\geq$  160 mmHg and diastolic blood pressure  $\geq$  100 mmHg who were uncontrolled on dual drug therapy with Telmisartan-Amlodipine or Telmisartan-Hydrochlorothiazide combinations were enrolled in this study. The treatment period was of 120 days and patients were administered once daily fixed dose combination of Telmisartan 40 mg, Amlodipine 5 mg and Hydrochlorothiazide 12.5 mg. Patients were evaluated on 30<sup>th</sup>, 60<sup>th</sup> and 120<sup>th</sup> days of treatment.

**Results:** There was statistically significant ( $p < 0.0001$ ) decrease in systolic blood pressure from baseline to 30<sup>th</sup>, 60<sup>th</sup> and 120<sup>th</sup> day of treatment mean $\pm$ SD (157.0 $\pm$ 8.68 mmHg vs 148.7 $\pm$ 8.19, 137.3 $\pm$ 7.84, and 127.0 $\pm$ 7.02 mmHg) respectively. Similarly the diastolic blood pressure (DBP) was significantly ( $p < 0.0001$ ) reduced from the baseline to the 30<sup>th</sup>, 60<sup>th</sup> and 120<sup>th</sup> day of treatment (100.0 $\pm$ 6.43 mmHg vs. 96.0 $\pm$ 6.21, 86.6 $\pm$ 6.06 and 80.6 $\pm$ 2.53 mmHg respectively).

**Conclusion:** Thus triple drug fixed dose combination of Telmisartan, Amlodipine and hydrochlorothiazide was found to be effective and safe option for the optimal management of hypertension.

**Keywords:** Diastolic, Systolic, Blood Pressure, Hypertension, Triple drug fixed dose combination

### INTRODUCTION

In developed and developing countries, uncontrolled blood pressure (BP) remains a major public healthcare problem. It is a major cardiovascular risk factor and contributes for cardiovascular mortality as well morbidity. Untreated hypertension leads to progressive rise in blood pressure, and often gives resistant state due to associated vascular and renal damage.<sup>1</sup>

It is a major risk factor for stroke (ischaemic and haemorrhagic), myocardial infarction, heart failure,

chronic kidney disease, peripheral vascular disease, cognitive decline and premature death.<sup>2</sup>

In India about 70% of coronary heart disease-related deaths occur in people younger than 70 years compared with 22% in the West and 94% stroke deaths occurs in people less than 70 years in contrast to 6% in developed countries.<sup>3</sup>

Evidence studies indicate that for every 20mmHg increase in systolic BP, or for every 10mmHg increase in diastolic BP, the risk of cardiovascular disease (CVD)

doubles. It has been observed in meta-analysis studies that every 20mmHg reduction in systolic BP reduces 40–45% chances of cardiovascular disease.<sup>4</sup> The European Society of Hypertension and the European Society of Cardiology, states that the primary goal of treatment is to achieve the maximum reduction in long-term total risk of cardiovascular morbidity and mortality.<sup>5</sup>

Monotherapy is effective in some patients but more than 50% patients require combination therapy for appropriate control of BP.<sup>6</sup> Targets are achieved in only a limited number of patients using monotherapy. Since the etiopathogenesis of hypertension is multifactorial, most patients require two or more antihypertensive agents with different mechanisms of action for the optimal management.<sup>5,7</sup> Even though combining two drugs may significantly improve efficacy and reduce the BP but more than 20% patients require combination therapy with three agents.<sup>7</sup> For patients with very-high baseline BP values or those at high Cardiovascular risk, European guideline recommends the combined use of a calcium channel blocker, an angiotensin II receptor blocker and a thiazide diuretic.<sup>8</sup>

This approach is also recommended by the Joint National Committee (JNC VIII) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure<sup>9</sup>

Poor patient compliance due to multiple pills can lead to failure of target BP goal set by JNC VIII (Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure). Fixed-dose single-pill combination therapies have been associated with better patient adherence & compliance<sup>10</sup>. This approach may facilitate better clinical outcomes, compared with traditional and time-consuming treatment with limited number of adverse events. This study was conducted to find out the efficacy and tolerability of fixed dose combination of Telmisartan, Amlodipine and Hydrochlorothiazide in the management of hypertension uncontrolled with dual drug therapy.

## METHODS

This study was a post marketing, non-randomized, open, non-comparative, mono centric study. The triple drug fixed dose combination of Telmisartan 40 mg, Amlodipine 5 mg and Hydrochlorothiazide 12.5 mg was administered to hypertensive patients once daily for 4 months (120 days). Informed consent was taken from the patients & the post marketing surveillance was in accordance with the principles in declaration of Helsinki and Good Clinical Practice (GCP).

### Inclusion Criteria

Both male and female hypertensive patients on dual therapy aged  $\geq 45$  years old with seated cuff  $\geq 160$  mmHg and DBP  $\geq 100$  mmHg and who were willing to give informed consent were included.

### Exclusion Criteria

Patients with any condition which in the opinion of the investigator makes the patient unsuitable for inclusion like; known or suspected secondary hypertension, history of asthma or angina, female patient who was pregnant or willing to get pregnant, and patients with known hypersensitivity to any of the ingredient of the fixed dose combination were excluded from the study.

### Patient Distribution

Out of 30 patients 18 were male and 12 were female patients in the age range of 45-70 years old (Table 1).

**Table 1: Baseline characteristics of all patients.**

Male/Female (n)	18/12
Age (yrs) range	45-70
Number of patients > 60 years	10
Number of patients < 60 years	20
SBP (Mean $\pm$ SD) mm Hg	157.3 $\pm$ 8.68
DBP (Mean $\pm$ SD) mm Hg	100.0 $\pm$ 6.43

### Efficacy and Safety Evaluations

To evaluate the Efficacy following parameters were observed.

**Primary outcome Measures:** Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were included in primary outcome, which were evaluated at 30<sup>th</sup>, 60<sup>th</sup> and 120<sup>th</sup> day of treatment.

**Secondary Outcome Measures:** Global assessment of efficacy and safety were included in this outcome. Investigator assessed the efficacy by using a three point scale as poor, good and excellent. Poor was for those patients, whose BP did not change from baseline, good when BP reduced by 15% from the baseline and excellent for those who achieved the target BP goal set by JNC VIII that is <150/90 for elder patients aged above 60 year and 140/90 for those aged less than 60 years.

Global assessment regarding safety was evaluated by recording any adverse event or any complaint during the therapy during every visit. Safety outcomes include mainly symptoms related to hypotension like blurred vision, confusion, dizziness, nausea, vomiting, weakness or any other untoward effects. Patients were interviewed and asked about the type of adverse events throughout the study.

### Statistical analysis

Data analysis on patient demographics and various outcome measures were performed using graph pad prism 6. Comparison between the baseline values with the value on the 15<sup>th</sup>, 30<sup>th</sup>, 60<sup>th</sup> and 120<sup>th</sup> day of treatment were

made, as well as comparison in between these days were made by applying one way analysis of variance & the Tukeys multiple comparison test. Value of P<0.05 were considered as significant.

**RESULTS**

SBP and DBP were recorded. In addition, overall efficacy and tolerability was assessed at the end of the study period. The baseline characteristics of patients are summarized in the Table 1.

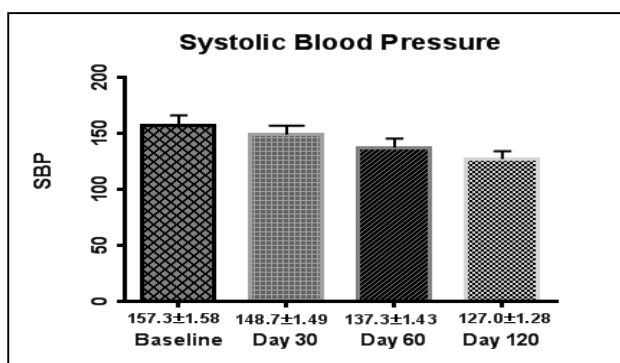
**Systolic Blood Pressure (SBP)**

The SBP was measured at base line and then subsequently at 30<sup>th</sup>, 60<sup>th</sup> and 120<sup>th</sup> days of treatment. The baseline SBP (Mean±SD) was 157.3±8.68 mmHg. The mean SBP at 30<sup>th</sup>, 60<sup>th</sup> and 120<sup>th</sup> days of treatment were 148.7±8.19 mmHg, 137.3±7.84 mmHg and 127.0±7.02 mmHg respectively. There was statistically highly significant (p<0.0001) decrease in SBP from the baseline to the 30<sup>th</sup>, 60<sup>th</sup> and 120<sup>th</sup> day of treatment (Table 2, Fig. 1). SBP decreased by -8.6±0.49 mmHg, -20.0±0.84 mmHg and -30.3±1.66 mmHg from the baseline to 30<sup>th</sup>, 60<sup>th</sup> and 120<sup>th</sup> day of treatment respectively (Table 4).

**Table 2: Effect of triple drug therapy on SBP.**

	Baseline	Day 30***	Day 60***\$	Day 120***\$
Mean± SD mmHg	157.3± 8.68	148.7± 8.19	137.3± 7.84	127.0± 7.02

\*\*\* p<0.0001 vs. baseline, \$ p<0.0001 vs. Day 30



**Figure 1: Systolic blood pressure.**

**Diastolic Blood Pressure (DBP)**

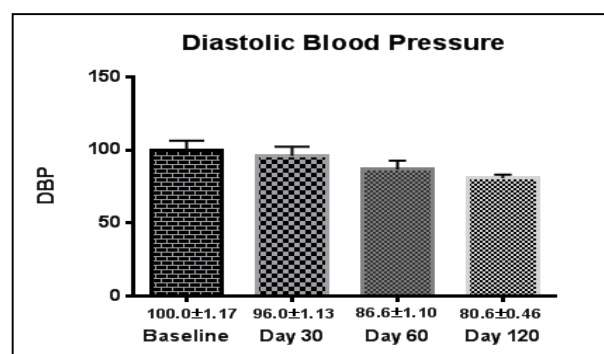
The DBP was measured at base line and then subsequently at 30<sup>th</sup>, 60<sup>th</sup> and 120<sup>th</sup> days of treatment. The baseline DBP (Mean±SD) was 100.0±6.43 mmHg. The mean DBP at 30<sup>th</sup>, 60<sup>th</sup> and 120<sup>th</sup> days of treatment were 96.0±6.21 mmHg, 86.6±6.06 mmHg and 80.6±2.53 mmHg respectively. There was statistically highly significant

(p<0.0001) decrease in DBP from the baseline to the 30<sup>th</sup>, 60<sup>th</sup> and 120<sup>th</sup> day of treatment (Table 3, Fig. 2). DBP decreased by -4.0±0.22 mmHg, -13.4±0.37 mmHg and -19.4±3.90 mmHg from the baseline to 30<sup>th</sup>, 60<sup>th</sup> and 120<sup>th</sup> day of treatment respectively (Table 4).

**Table 3: Effect of triple drug therapy on DBP.**

	Baseline	Day 30***	Day 60***\$	Day 120***\$
Mean± SD mmHg	100.0± 6.43	96.0± 6.21	86.6± 6.06	80.6± 2.53

\*\*\*p<0.0001 vs. baseline, \$ p<0.0001 vs. day 30<sup>th</sup>



**Figure 2: Diastolic blood pressure.**

**Table 4: Change in SBP and DBP from the baseline (Mean±SD mmHg).**

BP	Day 30	Day 60	Day 120
ΔSBP	-8.6±0.49	-20.0±0.84	-30.3±1.66
ΔDBP	-4.0±0.22	-13.4±0.37	-19.4±3.90

**Achievement of JNC VIII goal**

As per JNC VIII recommended target goal for patients >60 years old is 150/90 mmHg and 140/90 mmHg for patients of age <60 years. During and after the treatment following are the percentage of patients achieving the target BP goal (Table 5).

**Table 5: Percentage of patients achieving the target BP (<150/90 mmHg).**

	Day 30 % of patients (n)	Day 60 % of patients (n)	Day 120 % of patients (n)
Age>60	(03/10)	(09/10)	(10/10)
Years	30.00%	90.00%	100.00%
Age<60	(06/20)	(16/20)	(20/20)
Years	30.00%	80.00%	100.00%

**Global Assessment of Efficacy and Tolerability**

Efficacy evaluation was considered in three grades: Excellent, Good and Poor. On the 30<sup>th</sup> day of treatment

30.0% of patients in both the age group i.e. >60 years and <60 years showed efficacy as excellent. Similarly on 60<sup>th</sup> day of therapy 90.0% & 80.0% of patients aged >60 years & <60 years respectively showed efficacy as excellent. 100.00% of patients of age group >60 years & <60 years showed efficacy as excellent after the completion of study period of 120 days. No patients showed poor efficacy after the completion of study period of 120 days.

Treatment was well tolerated and 2 out of 30 patients (6.66%) complained about the side effects like headache, general weakness and dizziness.

## DISCUSSION

It is well known that the etiopathogenesis of hypertension is multifactorial and most of the patients require more than one antihypertensive drug to achieve target BP. Goal of Hypertension is to control BP with minimum complications and adverse effects that improve the patient's quality of life. European guidelines and many other guidelines suggest the need of fixed dose combination therapy for the treatment of hypertension.<sup>7,11</sup> On the basis of clinical studies using fixed dose combinations in a single pill represents a step forward in improving the control of hypertension and are efficient to achieve target goal of BP with no safety issues.<sup>12,13</sup>

Triple drug combination has synergistic and complementary mechanism of action and higher efficacy compared to monotherapy.<sup>11</sup> Ample evidences are available from the different clinical studies that multiple antihypertensive therapies are often required for effective control of blood pressure. Dose titration is allowed by triple combination therapy without increasing pill burden which allows patient compliance and adherence.<sup>14</sup>

A clinical benefit of triple drug combination in the management of hypertension has been already established. This study was conducted to evaluate the efficacy and safety of triple drug fixed dose combination of Telmisartan, Amlodipine and Hydrochlorothiazide.

A study conducted by S. Bhattacharya, on triple drug combination (ARB+CCB+Diuretic) in the management of hypertension with or without co morbidities for 120 days reported change in SBP/DBP from baseline to 60<sup>th</sup> & 120<sup>th</sup> day of treatment ( $p < 0.0001$ ) as  $-36.0 \pm 0.66 / -17.4 \pm 1.21$  mmHg and  $-41.0 \pm 6.16 / -22.5 \pm 0.25$  mmHg respectively. Results of the present study are comparable to the study conducted by S. Bhattacharya. The changes in SBP & DBP reported in this study are lower compared to results reported earlier by Bhattacharya. The higher reduction from baseline reported by Bhattacharya et al., could be due to higher baseline SBP & DBP in those patients.<sup>15</sup>

Regarding the achievement of target BP; present study showed high percentage of hypertensive patients achieving the target BP in comparison to previous studies. In a study

conducted by Khemchandani et al., use of same triple drug combination for 2 months (60 days) in the management of hypertension resulted in 65% and 85% of patients achieving the target BP at 30<sup>th</sup> and 60<sup>th</sup> day of treatment respectively. While in the present study 90.0% & 80.0% patients of age group >60 and <60 years old achieved the JNC VIII target at the 60<sup>th</sup> day of treatment respectively. This could be due to the difference in target BP achievement recommended by JNC VII & JNC VIII.<sup>9</sup>

A study conducted by Bhatt et al on triple drug combination ARB (angiotensin receptor blocker) + CCB (calcium channel blocker) + Diuretic in the management of hypertension with or without co morbidities for 120 days. The mean BP reduction at last visit compared with baseline was  $-43.0 \pm 4.4$  mmHg (SBP) and  $-11.8 \pm 4.3$  mmHg (DBP) which is comparable to present study result of 120<sup>th</sup> day. The value of SBP and DBP reduction at 120<sup>th</sup> day were found to be  $-30.3 \pm 1.66$  mmHg and  $-19.4 \pm 3.90$  mmHg from baseline respectively.<sup>16</sup> Results of the present study are either better or comparable to the previous studies.

Thus the results of this present study showed better or comparable to the results of the earlier study with regard to the reduction in both SBP/DBP and in the achievement of target goal. Side effects were mild in nature and did not require discontinuation of therapy. Overall no safety concern for treatment was identified.

## CONCLUSION

Triple drug fixed dose combination therapy of Telmisartan, Amlodipine and Hydrochlorothiazide is an effective, safe and convenient treatment approach in controlling the blood pressure and achieving the desired blood pressure goal according to JNC VIII with increased likelihood of patient adherence and compliance.

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