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ABSTRACT:

Despite many therapeutic options available only one-third of hypertensive patients achieve target Blood pressure (BP). The present study was undertaken to evaluate the efficacy and safety of triple drug, fixed dose combination of Telmisartan 40 mg + Amlodipine 5 mg + Hydrochlorothiazide 12.5mg, in the management of hypertensive patients with or without co-morbidities. A total of 60 patients were enrolled on the basis of mean seated cuff systolic blood pressure >160 mmHg and diastolic blood pressure >100 mmHg in this post-marketing surveillance (PMS) study. Patients were prescribed triple drug fixed dose combination for 120 days. In all groups (diabetic hypertensive, Dyslipidemic hypertensive and hypertension without any complication) there was statistically significant decrease ($p<0.0001$) in systolic blood pressure (SBP) from the baseline to 30th, 60th and 120th days of the treatment. Diastolic BP (DBP) was significantly decreased ($p<0.0001$) from the baseline just after 15th day of the treatment and on subsequent days of observation. 50% of diabetic hypertensive patients and 78.5% of hypertensive patients with dyslipidaemia achieved the Joint national committee VII (JNC VII) recommended goal (130/80mm Hg) at the end of study period of 120 days. Similarly in patients with hypertension without complication, 81.3% achieved the JNC VII recommended goal (140/90mm Hg) at the end of the study period. Triple drug fixed dose combination therapy of Telmisartan, Amlodipine and hydrochlorothiazide has been shown to be an effective, safe and convenient treatment strategy in controlling the blood pressure and achieving the desired blood pressure goal.

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

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INTRODUCTION:

Hypertension (HTN) is a major public health problem in India and globally [1]. It is a major risk factor for coronary events, stroke, heart failure, peripheral vascular disease, and progression of kidney disease [2] which lead to cardiovascular mortality. In spite of the many therapeutic options available only one-third of hypertensive patients achieve correct blood pressure (BP) levels [3]. Because the etiopathogenesis of hypertension is multifactorial, most patients require more than one antihypertensive drug to achieve correct BP [4]. In patients with high or very high cardiovascular risk, such as diabetics or those with renal failure, a combination of three or more antihypertensive drugs with different mechanisms of action is required to reach the desired BP goal (BP <130/80)[5].

The use of antihypertensive combinations with complementary mechanisms of action results in greater BP reductions than those achieved by the sum of each drug in monotherapy [6]. 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[5]. As demonstrated in various clinical studies concept of monotherapy up-titration to achieve BP target has been repetitively challenged. Such strategy is not likely to achieve the same BP-lowering effect in comparison to combination therapy [7]. In a recent meta-analysis, it was observed that the BP-lowering effect of combination drugs from two different classes was five times more than doubling the dose of a single drug [8].To achieve optimal, recommended BP targets set by Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) (i.e.130/80 mmHg for diabetic hypertensive & 140/90mmHg for hypertensive without any complication), most hypertensive patients requires a combination of two or more BP-lowering drugs, and monotherapy would likely be sufficient only in a small proportion of patients (about 20%–30%) [9]

Triple-combination formulations are emerging and may additionally offer the advantage of further reducing the pill burden [10]. In addition, single-pill combination (SPC) drugs have also gained opinion as the preferred approach to combine BP-lowering drugs in recently updated European guidelines [11]

The objective of this study was to evaluate the efficacy and tolerability of fixed-dose triple-combination of Telmisartan, Amlodipine and Hydrochlorothiazide in the management of hypertension.

SUBJECTS AND METHODS:

This was a post marketing surveillance (PMS), non-randomized, open, non-comparative, mono centric study conducted in a hospital based in Ahmedabad, India. Triple drug fixed dose

combination of Telmisartan 40 mg, Amlodipine 5mg and Hydrochlorothiazide 12.5mg was administered to hypertensive patients for 4 month (120 days). Informed consent was obtained from the patients & the post marketing surveillance was in accordance with the clinical principles laid down in declaration of Helsinki.

Inclusion Criteria

Both male and female patients aged ≥ 35 years willing to give informed consent were included. Basis of selection solely based on the seated cuff SBP and DBP value and was uncontrolled on dual therapy. Patients with seated cuff SBP 140–186 mm Hg and DBP 96–120 mm Hg were included in this study.

Exclusion Criteria

Patients were excluded from entry into the study if they had a known/suspected history of hypersensitivity to any of the drugs of the fixed dose combination, hepatic encephalopathy, and known cases of hepatic or renal insufficiency, pregnant or lactating women. In addition, patients with a history of coronary disease, congestive heart failure, or a recent acute cardiovascular event (previous 3 months) or stroke (previous 6 months) were excluded.

Patient distribution

A total of 60 patients were monitored in the study and entered into the final analysis. Out of 60 patients 32 were Male and 28 were female. Female patients were in the age range of 35-68 years and male patients were in the age range of 37-73 years old. The patients were categorized into three groups based on their medical history. The three groups were diabetic hypertensive (14) (23.3%), Hypertension with dyslipidemia 14 (23.3%) and hypertension without any complication 32 (53.3%) as shown in the Table 1.

Table 1: Distribution of Patients:

	Hypertension	Hypertension with diabetes	Hypertension with Dyslipidaemia
Number (%) of Patients	32 (53.3%)	14 (23.3%)	14 (23.3%)

Evaluation of primary outcome measure: the parameters recorded at baseline and on the 15th, 30th, 60th and 120th day of the study were systolic blood pressure, diastolic blood pressure

Evaluation of secondary outcome measure: Global assessment of efficacy and safety; efficacy was evaluated at the end of the study. Investigator assessed 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 changed by 15% from the baseline and excellent for those who achieved the target BP. Global assessment regarding safety was evaluated by recording any

adverse event or any complaint during the therapy in every visit.

Statistical analysis

Data analysis on patient demographics and various outcome measures were performed using graph pad prism 5 (software for statistical analysis). Comparison between the baseline values with the value on the 15th, 30th , 60th and 120th day of treatment were made, as well as comparison in between these days by applying one way analysis of variance & the Turkeys multiple comparison test. Values of $P < 0.05$ were considered as significant.

RESULTS

Diabetic Hypertensive group

The systolic blood pressure was recorded at the baseline and subsequently at 15th, 30th , 60th and 120th days of treatment. The baseline Mean ± Standard Deviation (SD) SBP was 158 ± 11.2 mmHg. The mean SBP at 15th, 30th, 60th and 120th days of the treatment were 153 ± 10.4 mmHg, 147±9.75 mmHg, 141±6.64 mmHg and 136±6.13 mmHg respectively (Table 2).

There was statistically significant decrease ($p<0.0001$) in the SBP from the baseline to 30th, 60th and 120th days of the treatment (Table No-02). Changes in SBP were 17 ± 4.56mmHg and 22±5.07 mmHg from baseline to 60th and 120th days of the treatment respectively.

Diastolic blood pressure (DBP) was recorded at the baseline and at 15th, 30th, 60th and 120th days of treatment. The mean DBP at baseline was 107 ± 6.21 mmHg and on 15th, 30th, 60th and 120th days of the treatment were 101 ± 5.13, 95.3 ± 4.61, 90.4 ± 3.25 and 85.3 ± 2.67 mmHg respectively. There was statistically significant decrease ($p < 0.0001$) in DBP from the baseline to 15th, 30th, 60th and 120th days of the treatment (Table 2). Changes in DBP were 12 ± 1.6mmHg, 16.6 ± 2.96mmHg and 21.7 ± 3.54mmHg from baseline at 30th, 60th and 120th days of the treatment respectively.

Table 2: Effect of triple drug therapy on Blood Pressure in Hypertension with diabetes

	Base line	15th Day	30th Day	60th Day	120th Day
SBP	158 ± 11.2	153 ± 10.4*	147±9.75***	141±6.64***	136±6.13***
DBP	107 ± 6.21	101 ± 5.13**	95.3±4.61***	90.4±3.25***^	85.3±2.67***^^

* $p<0.05$ vs Baseline, ** $p<0.01$ vs Baseline, *** $p<0.0001$ vs Baseline, ^ $p<0.05$ vs 30th Day, ^^ $p<0.0001$ vs 30th Day

At the end of the study period the BP in 7 of the 14 patients in the group was within the range 130/80 mmHg. This indicated that 50% of patients in the diabetic hypertensive group achieved the desired goal (130/80 mmHg) set by JNC VII.

Dyslipidemic Hypertensive group

Systolic blood pressure was recorded at the baseline and on subsequent 15th, 30th, 60th and

120th days of treatment. The baseline Mean ± Standard Deviation (SD) SBP was 160 ± 11.4 mmHg. The mean SBP at 15th, 30th , 60th and 120th days of the treatment were 155 ± 9.88, 150±9.97, 143±8.05 and 137±7.54 mmHg respectively (Table 3). There was significant decrease ($p<0.0001$) in systolic blood pressure from the baseline at 30th, 60th and 120th days of the treatment. Moreover there was significant decrease in systolic blood pressure between 15th day and 60th & 30th and 120th days of treatment. Changes in systolic blood pressure were 17±3.35 and 23±3.86 mmHg from baseline to 60th and 120th days of the treatment. Diastolic blood pressure at the baseline and on subsequent 15th, 30th, 60th and 120th days of treatment was recorded. The mean DBP was recorded at baseline was 107 ± 6.01 mmHg and on 15th, 30th , 60th and 120th days of the treatment were 100 ± 4.83, 95±3.74, 89.9±2.88 and 85.3±2.55 mmHg respectively (Table 3). There was significant decrease ($p<0.0001$) in diastolic blood pressure from the baseline at 15th, 30th, 60th and 120th days of the treatment. Changes in DBP were 12±2.27, 17.1±3.21 and 21.7±3.46 mmHg from baseline at 30th, 60th and 120th days of the treatment respectively.

Table 3: Effect of triple drug therapy on Blood Pressure in Hypertension with dyslipidaemia

	Base line	15th Day	30th Day	60th Day	120th Day
SBP	160±11.4	155±9.88	150± 9.97*	143± 8.05***	137± 7.54***^
DBP	107±6.01	100±4.83**	95±3.74***	89.9±2.88***^^	85.3±2.55***+

* $p<0.05$ vs Baseline, ** $p<0.01$ vs Baseline, *** $p<0.0001$ vs Baseline, ^ $p<0.05$ vs 30th Day, ^^ $p<0.0001$ vs 15th Day, + $p<0.0001$ vs 30th Day

At the end of the study period, the BP in 11 of the 14 patients in the group was within the range 140/90 mmHg. This indicated that 78.5% of patients of hypertension with dyslipidemia achieved the desired goal (140/90 mmHg) set by JNC VII.

Evaluation in Hypertensive without any complication

Systolic blood pressure was recorded at the baseline and on subsequent 15th, 30th, 60th and 120th days of treatment. The baseline Mean ± Standard Deviation (SD) SBP was 165 ± 12.2 mmHg. The mean SBP at 15th, 30th, 60th and 120th days of the treatment were 158 ± 11.2, 152±10.3, 146±9.59 and 140±8.13 mmHg respectively (Table 4). There was significant decrease ($p<0.0001$) in SBP from the baseline to 30th, 60th and 120th days of the treatment. Moreover there was significant decrease in systolic blood pressure from 15th day to 60th day & 30th to 120th days of treatment. Change in SBP was 19±2.61 and 25±4.07 mmHg from baseline

to 60th and 120th days of the treatment respectively.

Diastolic blood pressure at the baseline and on subsequent 15th, 30th, 60th and 120th days of treatment was recorded. The mean DBP was recorded at baseline was 106 ± 4.46 mmHg and on 15th, 30th , 60th and 120th days of the treatment were 97.7±15.2, 94.6±3.87, 89.4±3.08 and 84.4±3.09 mmHg respectively (Table 4). There was significant decrease ($p<0.0001$) in diastolic blood pressure from the baseline at 15th, 30th, 60th and 120th days of the treatment. Changes in DBP were 11.4±0.59, 16.6±1.38 and 21.6±1.37 mmHg from baseline at 30th, 60th and 120th days of the treatment.

Table 4: Effect of triple drug therapy on Blood Pressure in Hypertension with diabetes/dyslipidaemia

	Base line	15th Day	30th Day	60th Day	120th Day
SBP	165±12.2	158±11.2	152±10.3***	146±9.59***	140±8.13***^
DBP	106±4.46	97.7±15.2***	94.6±3.87***	89.4±3.08***	84.4±3.09***^

*** $p<0.0001$ vs Baseline, ^ $p<0.0001$ vs 30th Day

At the end of the study period 81.25% of patients in the hypertensive group achieved the desired goal (140/90 mmHg) set by JNC VII.

Global efficacy and safety evaluation

As per investigators assessment about overall efficacy of this triple drug fixed dose combination, which was assessed on the basis of investigators satisfaction in achieving the target blood pressure goal 140/90 mm Hg for hypertensive patients with or without dyslipidemia and 130/80 mmHg for diabetic hypertensives. Investigator assessed 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 changed by 15% from the baseline and excellent for those who achieved the target BP.

At the end of therapy, 15.6% (5/32) hypertensive patients without any complications showed good, 81.25% (26/32) of patient showed excellent efficacy and 3.12% (1/32) showed poor response. In diabetic hypertensive patients 50% (7/14) showed excellent and 35.7% (5/14) showed good while 14.2% (2/14) showed poor efficacy. In hypertensive patients with dyslipidemia 78.5% (11/14) excellent and 21.42% (3/14) showed good efficacy (Table 5). As per investigators assessment regarding the tolerability, which was assessed on the basis of any reported side effect resulting into discontinuation of therapy or compelling the use of concomitant drug to subside the side effects. In this study all the patients tolerated the triple drug therapy well and no side effects were reported.

Table 5: Effect of triple drug combination on efficacy in various groups

	Excellent Efficacy	Good Efficacy	Poor Efficacy
Hypertension	81.25%	15.6%	3.12%
Hypertension with Diabetes	50.0%	35.7%	14.28%
Hypertension with Dyslipidaemia	78.5%	21.42%	Nil

DISCUSSION

The different available fixed dose combinations of angiotensin receptor blocker (ARBs) / hydrochlorothiazide (HCTZ) and ARBs/Amlodipine have been shown to be efficient and safe in reducing BP levels in patients in whom monotherapy was not sufficient to achieve BP control [12, 13]. The possible use of triple therapy with Amlodipine, Telmisartan and HCTZ in a single pill represents a step forward in improving the control of hypertension by making treatment simpler and thereby improving long-term adherence and treatment persistence. It is proven that delaying BP control by strategies of increasing dose, increases the risk of cardiovascular events in comparison with the initial use of combinations [14].

In different clinical studies it has been observed that the efficacy of the triple combination is superior to that of its components in monotherapy or in dual combination.

In this study we evaluated the efficacy and safety of triple drugs fixed dose combination of Telmisartan 40 + Amlodipine 5mg+ Hydrochlorthiazide 12.5 mg in the management of hypertension in three groups of patients, diabetic hypertensive, dyslipidemic hypertensive and hypertension without any complication. Results of our study are comparable and supporting the results of earlier studies using the triple fixed dose combination in the management of hypertension.

A study conducted by Duprez D et al [15] have shown that after 6 weeks of the treatment reduction in systolic/diastolic ABP (ambulatory blood pressure) were greater in the triple combination (ARB/CCB/ HCTZ) group than in the dual therapy (ARB/HCTZ) group (-22.0/-13.3 versus -17.4/-8.1 mmHg). Similarly in our results after 60th day of the treatment msBP (mean seated blood pressure) reduction was -19/-16.6 mmHg which is comparable to this study. Another study conducted by Destro M et al, [16] after 8 weeks of the treatment reduction in msBP was -30.5/-13.8 mmHg while in our study reduction in msBP was -19/-16 and 25/-21.6 mmHg respectively at 60th day of treatment & after the completion of study. It is clear that in the present study reduction in DBP was better than the earlier study but the reduction in SBP was less. Moreover regarding achieving the target BP goal, a study conducted by Kereiakes DJ et al [17]

observed that after 16 weeks of study 79.8% of participants reached BP goal which is comparable to present study in which 81.25% patients achieved the target blood pressure goal after the completion of the study (120 days).

Regarding the efficacy of triple drug fixed dose combination in the diabetic hypertensives, there was significant reduction in SeBP and results of the present study is comparable to the previous study conducted by Kereiakes et al [18]. After 12 weeks of the treatment SeBP (seated BP) reductions was -37.9/-22.0 mm Hg while in the present study after 120th days of the treatment it was -22/21.7 mmHg.. Moreover more number of diabetic hypertensives achieved the desired goal in this study (50%) compared to the study conducted by Kereiakes et al. (41.1 %). In dyslipidemic hypertensive's there was significant decrease ($p<0.0001$) in SBP & DBP from the baseline. In this group 78.5% of patient achieved the desired target goal (140/90 mmHg) at the end of therapy. This result is comparable to the study conducted by Roth EM et al [19] used the triple drug fixed dose combination in obese hypertensive patients where 12 weeks of treatment lead to 62% of patients achieving the target BP.

CONCLUSION:

The triple drug fixed dose combination therapy of Telmisartan, Amlodipine & hydrochlorothiazide has been shown to be effective with excellent tolerability.

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