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EFFICACY & SAFETY OF ORAL TRIPLE DRUG COMBINATION OF TELMISARTAN, AMLODIPINE AND HYDROCHLOROTHIAZIDE IN THE MANAGEMENT OF NON-DIABETIC HYPERTENSION

Khemchandani D.¹ and * Arif A. Faruqui²

¹Bairagarh, Bhopal

²504-A, Rizvi Mahal, Waterfield Road, Bandra (W), Mumbai-50 E

*Author for Correspondence

ABSTRACT

Multiple drug regimens are increasingly recognized as a tacit requirement for the management of hypertension. 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 hypertension. 40 hypertensive patients with seating cuff systolic blood pressure 140-200 mmHg and diastolic blood pressure 90-120 mmHg were enrolled in the study. Patients were prescribed to take triple drug fixed dose combination for 60 days. Patients were evaluated on 15th, 30th and 60th day of the treatment. There was statistically significant decrease in Systolic blood pressure (174 ± 3.14 mmHg to 134 ± 1.18 mmHg) and Diastolic blood pressure (101 ± 1.33 mmHg to 84 ± 0.79 mmHg) from the baseline to the end of the study period of 60 days. 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.

Key Words: Systolic Blood Pressure, Diastolic Blood Pressure, Triple Drug, Fixed Dose

INTRODUCTION

Hypertension remains the leading cause of mortality and the third largest cause of disability in both developed and developing countries (Eduardo, 2009). Hypertension is a major risk factor for ischaemic and haemorrhagic stroke, myocardial infarction, heart failure, chronic kidney disease, cognitive decline and premature death. Untreated hypertension is usually associated with a progressive rise in blood pressure. The vascular and renal damage that this may cause can culminate into a treatment-resistant state (Hypertension, 2011). It has been observed in different trials that lower BP values are associated with better outcomes in a broad range of patients.

Approximately 65% of hypertensive patients need ≥ 2 antihypertensive agents to achieve blood pressure (BP) control. In the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT) and in the Losartan Intervention For Endpoint (LIFE) trials $>70\%$ and $>90\%$ respectively, required ≥ 2 antihypertensive agents to achieve desired BP goal set by JNC VII (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure). Complexity of the dosing regimen/number of drugs is related to patient non adherence to the therapy (Eduardo, 2009). So the triple drug therapy in a single pill is effective in the management of hypertension uncontrolled with the dual therapy. Clinically it has been observed that when Telmisartan is combined with Amlodipine and Hydrochlorothiazide, it showed better control of SBP and DBP (Maladkar *et al.*, 2012). Thus triple drug combinations are emerging as rational approach for the tight control of blood pressure and additionally offer the advantage of reducing the pill burden and improving compliance (De la Sierra and Barrios, 2012). This study was conducted to find out the efficacy and tolerability of fixed dose combination of Telmisartan-Amlodipine-Hydrochlorothiazide in the management of hypertension.

MATERIALS AND METHODS

This was post marketing, non-randomized, open, non-comparative, mono centric study conducted in a hospital based in Pune, India. The triple drug fixed dose combination of Telmisartan 40 mg plus

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Amlodipine 5 mg and Hydrochlorothiazide 12.5 mg, was administered to hypertensive patients for 60 days. Informed consent was obtained from the patients & the post marketing surveillance was in accordance with the principles laid down in declaration of Helsinki.

Inclusion Criteria

Both male and female hypertensive patients aged ≥ 25 years old with seated cuff SBP 140-200 mmHg and DBP 90-120 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, diabetes, 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

40 male and female hypertensive patients with seated cuff SBP 140-200 mmHg and DBP 90-120 mmHg were enrolled in the study. Out of 40 patients 29 were male and 11 were female patients.

At the time of entry into the study, base-line data of SBP and DBP were recorded. After informed consent was obtained, patients were prescribed to receive triple drug fixed dose combination of Telmisartan, Amlodipine and Hydrochlorothiazide once daily for 60 days. Patients were evaluated on 15th, 30th and 60th day of treatment and data on SBP and DBP were recorded.

Evaluation of Primary Outcome Measures

Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) were included in primary outcome, which were evaluated at 15th, 30th and 60th day of treatment.

Evaluation of Secondary Outcome Measures

Global assessment of efficacy and safety; efficacy was evaluated at the end of the study. 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 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 like DBP and SBP were performed using graph pad prism 6 (software for statistical analysis). Comparison between the baseline values with the value on the 15th, 30th, 60th day of treatment were made, as well as comparison in between these days by applying one way analysis of variance & Turkeys multiple comparison test. Value of $P < 0.05$ were considered as significant.

RESULTS AND DISCUSSION

Results

Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) was recorded. In addition, overall efficacy and tolerability was assessed at the end of the study period.

The baseline characteristics such as SBP and DBP of patients are summarized in the Table 1.

Table 1: Baseline characteristics of all patients

Baseline characteristics of all patients

Sex (Male/Female) ratio	29/11
Age (yrs) range	26-83
SBP (Mean \pm SEM)mm Hg	174 \pm 3.14
DBP (Mean \pm SEM)mm Hg	101 \pm 1.33

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Systolic Blood Pressure (SBP)

The SBP was measured at base line and then subsequently at 15th, 30th and 60th days of the treatment. The baseline SBP Mean±SEM was 174 ± 3.14 mmHg. The mean SBP at 15th, 30th, and 60th days of treatment were 159±2.81 mmHg, 143±2.23 mmHg and 134±1.18 mmHg respectively. There was statistically significant ($p<0.0001$) decrease in SBP from the baseline to the 15th, 30th, and 60th day of treatment (Table 2). Changes in SBP were 15± 0.33 mmHg, 31±0.91 mmHg and 40± 1.96 mmHg from the baseline to 15th, 30th and 60th day of treatment.

Table 2: Effect of triple drug therapy on SBP

	Baseline	Day 15**	Day 30***	Day 60***\$
Mean ± SEM	174 ± 3.14	159±2.81	143±2.23	134±1.18

** $p<0.001$ vs Baseline, *** $p<0.0001$ Vs. Baseline, \$ $p<0.01$ Vs 15th Day

Diastolic Blood Pressure (DBP)

The DBP was measured at base line and then subsequently at 15th, 30th and 60th days of the treatment. The baseline DBP Mean±SEM was 101±1.33 mmHg. The mean DBP at 15th, 30th, and 60th days of treatment were 93.6±1.13 mmHg, 88±1.06 mmHg and 84±0.79 mmHg respectively. There was statistically significant ($p<0.0001$) decrease in SBP from the baseline to the 15th, 30th, and 60th day of treatment (Table 3). Changes in DBP were 7.4± 0.2 mmHg, 13± 0.27 mmHg and 17 ± 0.54 mmHg from the baseline to 15th, 30th and 60th day of treatment respectively.

Table 3: Effect of triple drug therapy on DBP

	Baseline	Day 15***	Day 30***	Day 60***\$\$
Mean ± SEM	101±1.33	93.6±1.13	88±1.06	84±0.79

*** $p<0.0001$ Vs. Baseline, \$\$ $p<0.0001$ Vs 15th Day

Achievement of JNC VII Recommended Goal (140/90 mmHg)

JNC VII recommended target BP 140/90mmHg for hypertensive without any complication was achieved in 84% of the patients at the end of study.

Table 3: % of patients achieving the target BP (140/90 mmHg)

	30 th Day	60 th Day
% of patients achieving the JNC VII Recommended target BP	65%	85%

Global Assessment of Efficacy and Tolerability

As per investigators assessment about overall efficacy of triple drug fixed dose combination of Telmisartan, Amlodipine and Hydrochlorothiazide, assessed on the basis of 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 JNC VII recommended target BP.

On 30th day of treatment 65% (26/40) showed excellent efficacy, 30% (12/40) showed efficacy as good, and 5 % (2/40) showed poor efficacy. At the end of therapy i.e. 60th day of treatment 85% (34/40) showed excellent efficacy, 12.5% (5/40) showed efficacy as good, and 2.5 % (1/40) showed poor efficacy (Table 4).

Tolerability 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 therapy well and no side effects were reported.

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Table 4: Effect of triple drug combination on efficacy

	Excellent Efficacy	Good Efficacy	Poor Efficacy
30 th Day of treatment	65% (26/40)	30% (12/40)	5 % (2/40)
60 th day of treatment	85% (34/40)	12.5% (5/40)	2.5 % (1/40)

Discussion

Many trials have shown that BP normalization rate with rotational crossover monotherapy is less than 40% (Dickerson *et al.*, 1999). For this reason, most guidelines are agreeing that majority of patients need combination therapy and are now more frequently recommended (Mancia and Dominiczak, 2007; Gradman and Basile, 2011).

In different clinical studies the clinical benefits have been well established for triple combination in the effective management of hypertension; however this study was conducted to evaluate the efficacy and safety of triple drug fixed dose combination of Telmisartan 40 + Amlodipine 5mg+ Hydrochlorthiazide 12.5 mg in the management of hypertension uncontrolled with dual therapy.

Results of this study are in line with the studies conducted by various authors earlier. A study conducted by Destro *et al.*, (2010) on the use of triple drug combination for 8 weeks in the management of hypertension, have shown a significant (Destro *et al.*, 2010) reduction in mean seated blood pressure (msBP) by -30.5/-13.8 mmHg, which is almost similar to present study where at 30th and 60th day of treatment msBP was reduced by -31/-13 mmHg and -40/-17 mmHg respectively. It is clear that in the present study reduction in msBP at 30th Day is comparable to the results of 8th week and there was more reduction at 60th day of treatment (-40/-17 mmHg).

Regarding the achievement in target BP, 65% & 85% of patients achieved the JNC VII recommended target BP respectively at 30th and 60th day of treatment. A study conducted by Volpe *et al.*, (2012) on triple drug combination of ARB (angiotensin receptor blocker) + CCB (calcium channel blocker) + Diuretic, reported 70 % of patients achieving the target BP 140/90 after 10 weeks of the treatment (Volpe *et al.*, 2012).

Similarly in another study conducted by Roth *et al.*, (2013) on triple drug combination (ARB+CCB+Diuretic) in obese participants reported 62% of patients achieving the target BP after 12 weeks of the treatment. In the same study systolic blood pressure reduction and goal attainment was maintained through week 52 (Roth *et al.*, 2013). But in this study 65% of patients achieved the target much earlier i.e, after 30th day of treatment and was even higher at the end of therapy (85%). Thus the results of the present study are better than that of earlier study in terms of reduction in SBP, DBP and achievement in the target BP. Treatment was well tolerated and no safety concerns for treatment were identified.

Conclusion

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.

Author's Contributions

Dr. AAF contributed to prepare the protocol, case record form and conceptualized the study & interpreted the statistical data to prepare the manuscript.

Dr. KD conducted the study and shared the entire data for further analysis and interpretation.

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