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EFFICACY AND SAFETY OF TRIPLE DRUG FIXED-DOSE COMBINATION OF TELMISARTAN, AMLODIPINE AND HYDROCHLOROTHIAZIDE IN THE MANAGEMENT OF HYPERTENSION

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ABSTRACT:

Hypertension is a major health problem in India. Different clinical studies have reported that reducing the blood pressure can substantially decrease cardiovascular risk and all cause mortality. This study was conducted to evaluate the efficacy and safety of triple drug fixed dose combination of Telmisartan 40 mg, Amlodipine 5 mg and Hydrochlorthiazide 12.5mg. 41 hypertensive patients having systolic blood pressure ≥ 160 mmHg and diastolic blood pressure ≥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 Hydrochlorthiazide 12.5mg. Patients were evaluated on 15th, 30th, 60th and 120th days of treatment. There was statistically significant ($p<0.0001$) decrease in systolic and diastolic blood pressure from baseline to 15th, 30th, 60th and 120th days of treatment. At the end of the study period of 120 days 95.6% & 94.4% patients of age group >60 years and <60 years achieved the JNC VIII recommended target goal respectively. This triple drug fixed dose combination of Telmisartan, Amlodipine and hydrochlorothiazide was found to be effective and safe option for the optimal management of hypertension without any safety concern.

Keywords: Diastolic pressure, Systolic pressure, Hypertension, combination, Telmisartan, Amlodipine, Hydrochlorothiazide

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INTRODUCTION:

Hypertension is a major health problem in India. It is a major risk factor for cardiovascular disease and contributes significantly to cardiovascular morbidity and mortality. Different clinical studies have reported that reducing BP (blood pressure) can substantially decrease cardiovascular risk and all cause mortality [1]. Clinical studies have shown that every 20 mmHg increase in systolic blood pressure (SBP), or 10 mmHg increase in diastolic blood pressure (DBP), doubles the risk of cardiovascular disease (CVD). It has been observed in meta-analysis that every 20mmHg reduction in SBP can result in 40–45% reduction in cardiovascular disease [2]. Thus for the optimal management of hypertension and for the prevention of cardiovascular morbidity and mortality the goal of therapy is directed to reduce BP effectively. Ample evidences are available from the different clinical studies that multiple antihypertensive therapies are often required for effective control of BP. Although monotherapy is effective in some patients, over 50% of patients may require combination therapy for appropriate control of BP [3]. Based on cumulative data from different clinical trials, it has been estimated that at least 25% of patients require triple combination therapy to achieve BP control [4].

Multiple pills are the most important reason of poor adherence and posses the big challenge in achieving the 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 and compliance [5]. This approach may facilitate better clinical outcomes, compared with traditional and time-consuming stepped care and add on algorithms in the management of hypertension.

This study was conducted to find out the efficacy and tolerability of fixed dose combination of Telmisartan, Amlodipine and Hydrochlorothiazide in the management of Stage 2 hypertension.

SUBJECTS AND METHODS:

This was a post marketing, non-randomized, open, non-comparative study which was conducted in Kolkata. 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) who were uncontrolled on dual drug therapy with Telmisartan-Amlodipine or Telmisartan-Hydrochlorothiazide combinations. Informed consent was obtained from the patients and the post marketing surveillance (PMS) was in accordance with the principles in declaration of Helsinki and Good Clinical Practice (GCP).

Inclusion Criteria:

Both male and female hypertensive patients who were uncontrolled on dual drug therapy with Telmisartan-Amlodipine or Telmisartan-Hydrochlorothiazide combinations, aged ≥ 45 years old with mean seated cuff SBP (systolic blood pressure) ≥160 mmHg and DBP (diastolic blood pressure) ≥100 mmHg and who were willing to give informed consent were included in this study

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 with kidney and liver failure were also excluded from the study.

Patient Distribution:

A total of 41 patients of age range 45-75 years old were included in this study. Out of 41 patients 26 (63.4%) were male and 15 (36.6%) were female patients (Table 1).

Efficacy and Safety Evaluations:

There were two outcome variables to evaluate the Efficacy: Primary outcome and Secondary outcome.

Primary outcome Measures: SBP and DBP were included in primary outcome, which were evaluated at 15th, 30th, 60th and 120th day of treatment.

Secondary Outcome Measures: Global assessment of efficacy and safety 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 slightly changed from baseline and in the range of 0-5%, good when BP changed by 15% from the baseline and excellent for those who achieved the target BP goal set by JNC VIII which are <150/90 mmHg for elder patients aged above 60 year and 140/90 mmHg for those aged less than 60 years.

Global assessment regarding safety was evaluated by recording any adverse event or any complaint during the therapy in every visit. Safety outcomes include mainly symptoms related to hypotension like blurred vision, confusion, dizziness, nausea or vomiting, weakness and others. Patients were interviewed and asked about the appearance of any adverse events at every visit throughout the study period of 120 days.

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 15th, 30th, 60th and 120th day of treatment were

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

Table 1: Baseline characteristics of patients

Baseline characteristics of patients	
Males	26 (63.4%)
Females	15 (36.6%)
Age range	45 – 75 years
Number patients over 60 years	23 (56.1%)
Number patients below 60 years	18 (43.9%)
SBP (Mean ± SD) mm Hg	171.0 ± 8.89
DBP (Mean ± SD) mm Hg	100.0 ± 4.30

RESULTS:

SBP and DBP were recorded at baseline and at every visit throughout the study period of 120 days. 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 15th, 30th, 60th and 120th days of treatment. The baseline SBP Mean ± SD was 171.0 ± 8.89 mmHg. The mean SBP at 15th, 30th, 60th and 120th days of treatment were 163.0 ± 7.34mmHg, 146.0 ± 8.82 mmHg, 135.0 ± 8.23 mmHg and 130.0 ± 2.73 respectively. There was statistically significant (p<0.0001) decrease in SBP from the baseline to the 15th, 30th, 60th and 120th day of treatment (Tables 2 and 3). SBP decreased by 8.0 ± 1.55 mmHg, 25 .0 ± 0.07 mmHg, 36.0 ± 0.66 mmHg and 41.0 ± 6.16 mmHg from the baseline to 15th, 30th, 60th and 120th day of treatment respectively.

Table 2: Effect of triple drug therapy on systolic blood pressure

	Baseline	Day 15***	Day 30***	Day 60***^	Day 120***^
Mean ± SD mmHg	171.0 ± 8.8	163.0 ± 7.3	146.0 ± 8.8	135.0 ± 8.2	130.0 ± 2.7

*** p<0.0001 vs. baseline, ^ p<0.0001 vs. Day 30

Table 3: Change (∆) in SBP from baseline

	Day 15	Day 30	Day 60	Day 120
∆ SBP from baseline (mmHg)	-8.0 ± 1.55	-25.0 ± 0.07	-36.0 ± 0.66	-41.0 ± 6.16

Diastolic Blood Pressure (DBP):

DBP was measured at base line and then subsequently at 15th, 30th, 60th and 120th days of treatment. The baseline DBP Mean ± SD was 100.0 ± 4.30 mmHg. The mean DBP at 15th, 30th, 60th and 120th days of treatment were 92.9 ± 3.64 mmHg, 87.0 ± 4.32 mmHg, 82.6 ± 3.09 mmHg and 77.0 ± 4.05 respectively. There was statistically significant (p<0.0001) decrease in DBP from the baseline to the 15th, 30th, 60th and 120th day of treatment (Tables 4 and 5). DBP decreased by 7.1 ± 0.66 mmHg, 13.0 ± 0.02 mmHg, 17.4 ± 1.21 mmHg and 22.5 ± 0.25 mmHg from the baseline to 15th, 30th, 60th and 120th day of treatment respectively.

Achievement of JNC VIII goal:

Target BP goal is set by JNC VIII based on age and complications. 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 (Tables 6 and 7).

Table 4: Effect of triple drug therapy on DBP

	Baseline	Day 15***	Day 30***	Day 60***^	Day 120***^
Mean ± SD mmHg	100.0 ±4.30	92.9±3.64	87.0±4.32	82.6±3.09	77.5±4.05

***p<0.0001 vs. baseline, ^p<0.0001 vs. day 30th

Table 5: Change (∆) in DBP from the baseline

	Day 15	Day 30	Day 60	Day 120
∆ DBP from baseline (mmHg)	-7.1 ± 0.66	-13.0 ± 0.02	-17.4 ± 1.21	-22.5 ± 0.25

Table 6: Percentage of patients (>60 years) achieving the target BP (<150/90 mmHg)

	Day 30	Day 60	Day 120
% of patients (n)	(17/23) 73.9%	(21/23) 91.3%	(22/23) 95.7%

Table 7: Percentage of patients (<60 years) achieving the target BP (<140/90mmHg)

	Day 30	Day 60	Day 120
% of patients (n)	(12/18) 66.7%	(16/18) 88.9%	(17/18) 94.4%

Global Assessment of Efficacy and Tolerability:

As discussed in Efficacy and Safety Evaluations, Efficacy was considered in three grades: Excellent, Good and Poor. On the 30th day of treatment 73.9% and 66.7% of patients of age group >60 years and <60 years respectively showed efficacy as excellent. Similarly on 60th day of therapy 91.3% & 88.9% of patients aged >60 years and <60 years respectively showed efficacy as excellent. 95.7% and 94.4% of patients of age group >60 years and <60 years respectively showed efficacy as excellent after the completion of study period of 120 days. Overall clinical efficacy as good and poor on 30th and 60th day of treatment without regarding the age differentiation were 19.5% (8/41) and 7.3% (3/41) respectively. Only 4.8% (2/41) of patients showed poor efficacy after the completion of study period of 120 days. Moreover 2 out of 41 patients complained about the side effects mainly related with the symptoms of hypotension which were mild in nature and do not warn the safety concern.

DISCUSSION:

Different clinical studies using fixed dose combinations of angiotensin receptor blocker (ARBs) / hydrochlorothiazide (HCTZ) and ARBs/Amlodipine (Calcium channel blocker: CCB) have been shown to be efficient and safe in reducing BP [6,7]. Moreover 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 therapy [8]. Ample evidences are available from the different clinical studies that multiple antihypertensive therapies are often required for effective control of blood pressure. European guideline and many more guideline suggest the need of fixed dose combination therapy for the treatment of hypertension [9,10]. Based on cumulative data from different clinical trials, 25% of patients required triple drug combination therapy to achieve target BP [11].

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. The results of the present study are in line with the results of previous studies [12,13,14].

A study conducted by Duprez D et al [12] has shown that after 6 weeks (42 days) of 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 vs. -17.4/-8.1 mmHg). Similarly in the present study at 30th and 60th day of treatment reduction in systolic/diastolic blood pressure were 25.0 ± 0.07 / 13.0 ± 0.02 and 36.0 ± 0.66 / 17.4 ± 1.21 mmHg respectively. Thus the results of the present study on 30th day are comparable or even better than the result of the above mentioned study after 6 weeks of treatment.

Another study conducted by Abhichandani et al [13] 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 60th and 120th day of treatment ($p<0.0001$) as -19.0 ± 2.61 / -16.6 ± 1.38 mmHg and -25.0 ± 4.07 / -21.6 ± 1.37mmHg respectively. Results of the present study are better than the study conducted by Abhichandani et al (-36.0 ± 0.66 / -17.4 ± 1.21mmHg vs. -19.0 ± 2.61 / -16.6 ± 1.38 and -41.0 ± 6.16 / -22.5 ± 0.25 vs. -25.0 ± 4.07 / -21.6 ± 1.37mmHg) at 60th and 120th days of treatment respectively [13].

A study conducted by Maladkar et al used the same triple drug combination for 12 weeks in the management of hypertension [14]. There was statistically significant decrease in SBP/DBP from baseline to 12th week (end of the treatment) of treatment mean ± SD (165.7 ± 15.66 / 100.2 ± 10.31 mmHg vs. 122.5 ± 9.38 / 79.4 ± 6.64 mmHg). Similarly the present study reported statistically significant ($p<0.0001$) decrease in SBP/DBP from baseline to the end of 120th days (171.0 ± 8.89 / 100.0 ± 4.30 mmHg vs. 130.0 ± 2.73 / 77.5 ± 4.05 mmHg). Thus the results of the present study are comparable to the studies done earlier.

Regarding the achievement of target BP; the present study reported higher 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 30th and 60th day of treatment respectively [15]. While in the present study 91.3% and 88.8% of patients of age group >60 and <60 years old achieved the JNC VIII target at the 60th day of treatment respectively.

In the current study treatment was well tolerated but 2 out of 41 patients (4.8%) complained about the side effects like headache, general weakness and dizziness. Side effects were mild in nature and did not require discontinuation of therapy.

Our data indicates that triple drug combination was highly effective in achieving the target blood pressure without any major adverse event.

CONCLUSION:

Triple drug fixed dose combination therapy of Telmisartan, Amlodipine and Hydrochlorothiazide is an effective, safe and convenient treatment approach in achieving the target blood pressure goal in hypertensive patients.

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