INTERNATIONAL JOURNAL OF CLINICAL PHARMACOKINETICS AND MEDICAL SCIENCES

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Assessment of safety and efficacy of Telmisartan, Amlodipine and Chlorthalidone combination in stage 2 hypertension patients: A prospective observational study

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Article History:

Received on: 15 Feb 2021

Revised on: 24 Feb 2021

Accepted on: 26 Feb 2021

Keywords:

Telmisartan,
Amlodipine,
Chlorthalidone,
Combination therapy

ABSTRACT

Hypertension is a common and high incidence disease over the global population. The prevalence rate was going up as time passes and many treatment options were developed to compress this condition. However, we have a lot of treatment choices, the studies were going still on the effectiveness and suitability issues of antihypertensive drug regimens. This study aimed to assess the safety and efficacy of the triple-drug combination (Telmisartan, Amlodipine, Chlorthalidone) therapy regimen in stage 2 hypertensive patients and so that the obtained results provide a novel treatment or fixed dosage for hypertensive management. The resulting therapy will significantly maintain the BP levels to tolerate the patient's condition.

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eISSN: 2583-0953

DOI: <https://doi.org/10.26452/ijcpms.v1i1.185>

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INTRODUCTION

Hypertension or high blood pressure is a common condition that may lead to complicated health problems such as the increased risk of cardiovascular problems results in morbidity and mortality which are directly correlated with increased blood pressure. High blood pressure (BP) is the most widespread chronic disease in India and its occurrence is rapidly increasing among urban and rural populations triggered by many factors eventually. In India, nearly 70% occurrence of coronary artery heart disease-related deaths occur in people younger than 70 years compared with 22% in the West, and 94% of stroke deaths occur in people less than 70 years, and comparing 6% occurs in developed countries [1]. If hypertension is untreated

and there is a gradual rise in blood pressure, then it reaches the resistant state due to associated vascular and renal damage [2]. Hypertension is a major risk factor for cardiovascular conditions like MI, angina, heart failure, renal failure, early death rates due to cardiovascular complications [3]. Asian Patients have a greater risk of stroke than CAD in comparison to the population of western countries [4, 5]. Hypertension is often described as "the silent killer" because there is no appearance of any symptoms until serious complications were developed.

General introduction of Blood pressure

Blood pressure (BP) is the pressure exerted by the blood on the walls of the blood vessels flowing through them. Blood pressure in the blood vessels varies based on the type of blood vessels and the distance from the heart. The blood pressure in the vessels is based on the following.

- Heart distance from a particular blood vessel and
- Blood vessel nature.

Blood vessels are of two types: Arteries and Veins. Blood pressure is more in arteries than in the veins. Because the arteries walls are thicker and less elastic, while the walls of the veins are less thick and more elastic. The normal blood pressure is 120/80 mm Hg and in which 120 mm Hg is the systolic BP

and 80 mm Hg is known to be diastolic. Blood pressure is more during systole when compared to diastolic blood pressure. The difference between systolic and diastolic blood pressure is about 40 mm Hg and is known as pulse pressure (PP) and the ratio between the systolic, diastolic, pulse pressure is about SBP: DBP: PP = 3:2:1 [6].

Mean Arterial Blood Pressure

The mean arterial pressure is the average blood pressure in an individual in the single cardiac cycle.

$MAP = (Cardiac\ Output \times Systemic\ Vascular\ Resistance) + (Central\ Venous\ Pressure).$

Physiological variations of B.P.

1. Age: Adults have more blood pressure than children.
2. Sex: Blood pressure is more in males than in females.
3. Childbearing period: BP is more in the women bearing a child.
4. Altitude: Blood pressure is more in people living at higher altitudes.
5. Exercise: Exercise increases systolic blood pressure.
6. Emotion conditions: During emotions, there is a rise in blood pressure [7].

The factors that may alter Blood Pressure

1. The blood volume in the body.
2. Contractility of the heart.
3. Heart rate.
4. Blood flow and its state viscosity.
5. The medium of the blood (nature).
6. Blood vessels through which blood flows [8].

Factors provoking hypertension

- a) Age and sex: Age is the main factor and BP mainly rises with the increase in age and more in middle-aged and thereafter.
- b) Weight: Obese patients have higher chances of developing hypertension.
- c) Social history: smokers and alcoholics tend to have greater chances of developing hypertension.
- d) Diet: Dietary habits of the person, mainly the consumption of salt and other dietary intakes having

high sodium content (more than 8-10 gm per day) can cause hypertension because sodium can promote the rigidity of blood vessels.

e) Genetic predisposition: Genetics plays an important role in the development of hypertension.

The types of hypertension are classified into 5 categories and listed in Table 1.

Figure 1: Distribution of patients based on drug response who on AMLO-5mg and TELMA-80mg

Figure 2: Distribution of patients based on drug response who on AMLO-10mg and TELMA-80mg

MATERIALS AND METHODS

To evaluate the efficacy of telmisartan 80mg + Amlodipine 10/5mg+chlorthalidone 12.5mg in hypertension patients not responding to 4 weeks of dual therapy with telmisartan 80mg+amlodipine 10/5mg the below materials and methods are followed:

Study design

A Prospective and observational study.

Area of the study

Department of general medicine, ACSR govt medical college and hospital, Nellore.

This study was conducted to determine the safety and efficacy of antihypertensive drugs with dual therapy and triple therapy and also to decrease mortality rates and complications in hypertension patients and to improve their health-related quality of life.

Duration of the study

Six months from August 2018 to January 2019.

Table 1: Types of hypertension

S.NO	Category	Systolic pressure mmHg	Diastolic blood pressure mmHg
1	Normal	90-119	60-79
2	Pre-hypertension	120-139	80-89
3	Stage 1	140-159	90-99
4	Stage 2	≥160	≥100
5	Isolated Hypertension	≥140	<90

Table 2: Side effect profile of antihypertensive drugs in the present study

Side effects	Males	Females
Difficulty breathing	1	2
Dizziness	1	3
Angioedema	0	2
Pedal edema	4	1
Weakness	1	2
Giddiness	2	1
Tachycardia	1	0

Table 3: Data based on mean systolic and diastolic pressure during their 1ST 2ND and 3RD visits

Visit	Mean SBP	Mean DBP
Visit I	166.22 mm/Hg	109.25 mm/Hg
Visit II	138.95 mm/Hg	92.45mm/Hg
Visit III	128.65 mm/Hg	81.75 mm/Hg

Table 4: Data based on the effect of therapy on systolic and diastolic blood pressure

	Baseline	Visit2	Visit3
Mean SBP ± SD mmHg	166.25±6.24	138.95±9.37	128.65±8.4
Mean DBP ± SD mmHg	109.25±4.2	92.45±4.91	81.75±2.61

Size of sample

60 patients.

Patient enrolment

Patients are enrolled in the study based on inclusion and exclusion criteria.

Study method

A Prospective observational study in which patients who are diagnosed were selected and patients having DBP between 105-109 and 110-115 mm of hg was initiated with (telmisartan 80mg + amlodipine 5/10mg) and followed respectively. The patients who were not responded to dual therapy were selected and then they are given triple therapy containing three drugs (telmisartan 80mg + amlodipine 5/10mg +chlorthalidone 12.5 mg) and followed respectively.

Informed consent was taken from the patients & the

study and the purpose of our study was explained to the patient.

Inclusion criteria

1. Participants willing to sign an informed consent form indicating that they understand the purpose and the procedures required for the trial and are willing to participate in it
2. Male and male treatment patients aged 18-80 years with the diagnosis of stage-2 essential hypertension (DBP 105-120 mm of Hg and SBP 160-199mm of Hg) at the entry. Who is considered appropriate for initial dual therapy with telmisartan 80 mg +amlodipine 10/5 mg?
3. Patients who have inadequate BP control (DBP less than 90 mmHg) but have been shown at least 2mm DBP reduction after 4 weeks of dual

therapy will be selected for treatment allocation of triple therapy /dual therapy.

Exclusion criteria

1. Patients with secondary hypertension.
2. History of alcohol/drug abuse.
3. History of active Hepatitis-B/C within the past 3 months.
4. History of seizure disorder/epilepsy.
5. History of allergy /hypersensitivity to telmisartan/chlorthalidone/amlodipine/any other ARB/thiazides/CCBs
6. Participants with acute/severe bronchial asthma
7. Patients with renal/hepatic diseases (based on known lab abnormalities/ serum electrolytes abnormalities.
8. Patients with angioedema.
9. Pregnant /breastfeeding women and women of childbearing age not using an adequate method of contraception.

Study materials

1. The patient data collection form
2. Patient informed consent form

Process of the study

Patients who are with denovo primary hypertension were taken into the study along with their demographic details. In this study, we selected 60 denovo hypertensive patients based on diastolic blood pressure before initiating the therapy BP was recorded and were divided into 2 groups.

- 1) The patients with diastolic blood pressure between 105-109 mm/Hg have initiated with Telmisartan 80mg and Amlodipine 5mg.
- 2) The patients with diastolic blood pressure above 110 mm/Hg have initiated with Telmisartan 80mg and Amlodipine 10mg.

Statistical Analysis

Data will be recorded on a predesigned perform and managed using Microsoft Excel worksheets. All the entries will be double-checked for any possible error. The further data will be assessed and analyzed by using an appropriate statistical tool.

RESULTS

In our study total of 60 patients were included, based on inclusion and exclusion criteria, and those who are willing to sign the informed consent form were included in the study. Initial screening at the visit was done to check the inclusion and criteria needs. The patients who are eligible for the study were taken and the baseline systolic blood pressure and diastolic blood pressure were recorded, patients. Patients were categorized based on the diastolic blood pressure of the patients, the patients with diastolic blood pressure above 105 mmHg were included in the study. In our study total of 60 HYPERTENSIVE PATIENTS were enrolled, among them 33 (55%) are males and 27 (45%) are females.

Distribution of patients

1. Based on age groups of total hypertensive patients, males between 20-30 yrs (3.03%), 31-40 yrs (3.03%), 41-50yrs (30.30%), 51-60 yrs (39.39%), 61-70 yrs (21.21%), >70 yrs (3.03%) and females between 20-30 yrs (0%), 31-40 yrs (11.11%), 41-50yrs (37.03%), 51-60 yrs (14.81%), 61-70 yrs (22.22%), >70 yrs (14.81%).
2. Based on their blood pressure the patients who are with diastolic blood pressure between 105-109 mm/Hg have given telmisartan 80mg and amlodipine 5mg and the patients with diastolic blood pressure above 110 mm/Hg were initiated with telmisartan 80 mg and amlodipine 10 mg and the patients were informed to attend for follow up after 28 days of the treatment and the blood pressure were recorded. The blood pressure goals in patients were based on JNC VIII classification and the target diastolic blood pressure that has to be achieved after the initiation of therapy was to be less than 90 mmHg.
3. Based on drug response of the patients on AMLO-5mg & TELMA-80mg represented clearly in Figure 1 and AMLO-10 mg & TELMA-80mg represented in Figure 2. Side effects occurred due to therapy are listed in Table 2.

SBP and DBP were recorded. Besides, overall efficacy and tolerability were assessed during the study period. The baseline characteristics of patients are listed in Table 3 and Table 4.

DISCUSSION

In this study total of 60 patients were enrolled into the study according to inclusion criteria and exclusion criteria and those willing to give the informed

consent form. At the initial screening visit, SBP and DBP were recorded.

Patients are categorized based on the DBP and that DBP is between 105 to 109 mm of hg are treated with telmisartan 80mg, amlodipine 5mg and those DBP is more than 109 mm of hg treated with telmisartan 80mg, amlodipine 10mg.

After 28 days of the treatment diastolic blood pressure was recorded for all the patients and observed that out of 60 patients, 40 patients were responded to the treatment of dual therapy and their blood pressure was controlled or reduced. The remaining 20 patients' DBP was not controlled, hence these patients were considered as nonresponders and they were prescribed for triple therapy of telmisartan 80mg, amlodipine 10mg, and chlorthalidone 12.5mg up to the next visit. At visit 3, DBP was recorded for all patients who received triple therapy and observed that reduced DBP as per the JNC guidelines.

On comparing our study with the study conducted by Maccha S. Balraj, [8] on Efficacy and safety of the triple-drug fixed-dose combination of telmisartan 40mg, amlodipine 5mg, and hydrochlorothiazide 12.5mg in the management of hypertension we found that reduction in diastolic blood pressure was achieved from baseline DBP of mean $\pm$ SD (100.0 $\pm$ 6.43 mmHg to 96.0 $\pm$ 6.21, 86.6 $\pm$ 6.06 and 80.6 $\pm$ 2.53 mmHg) on successive measurement during 1st 2nd and 3rd visits respectively BUT in our study, the achievement of diastolic blood pressure was found to be mean $\pm$ SD (109.25 $\pm$ 4.2mmHg to 92.45 $\pm$ 4.91, 81.75 $\pm$ 2.61 mmHg) on 1st and 2nd visits respectively which states that achievement of DBP was early which is maybe due to increased dose of telmisartan and amlodipine i.e. 80mg and 10mg in our study which was found to be statistically significant ($p < 0.0001$).

On comparing our study with another study conducted by Subrato Bhattacharya [9] on efficacy and safety of the triple-drug fixed-dose combination of telmisartan, amlodipine, and hydrochlorothiazide in the management of hypertension we found that statistically significant decrease in DBP from baseline to 12th week (end of the treatment) of treatment mean $\pm$ SD (100.2 $\pm$ 10.31 mmHg vs. 79.4 $\pm$ 6.64 mmHg). But in our study, we achieved from baseline to mean $\pm$ SD (92.45 $\pm$ 4.91, 81.75 $\pm$ 2.61 mmHg) in 60 days which is statistically significant ($p < 0.0001$).

Regarding the achievement of target BP, the present study reported a higher percentage of hypertensive patients achieving the target BP in comparison to previous studies.

CONCLUSION

From our study, we concluded that the Triple regimen containing telmisartan 80mg amlodipine 10 mg and chlorthalidone 12.5 mg was more efficacious and effective over dual therapy which contains telmisartan 80 mg and amlodipine 5/10 mg in controlling and achieving the target blood pressure based on JNC VIII guidelines. The reasons behind inadequate control of blood pressure in patients using dual therapy may be due to several reasons which may include patient complies the given medication, concurrent disease states like pheochromocytoma, or maybe due to the discontinuation of therapy due to the side effects Like angioedema, pedal edema, dizziness, reflex tachycardia, giddiness, absorbed in the patients.

Funding Support

The authors declare that they have no funding support for this study.

Conflict of Interest

The authors declare that there is no conflict of interest.

Ethical Issues

Written informed consent was obtained from all the study subjects and the subjects were willing to participate in the study, information about socio-demographic characteristics was collected through the Telecommunication method.

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Cite this article: Mahesh Kumar P, Prathibha R. Assessment of safety and efficacy of Telmisartan, Amlodipine and Chlorthalidone combination in stage 2 hypertension patients: A prospective observational study. *Int. J. of Clin. Pharm. Med. Sci.* 2021; 1(1): 17-22.

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