International Journal of Pharmacology and Clinical Research (IJPCR)

IJPCR |Volume 3 | Issue 2 | July - Dec - 2019
www.ijpcr.net

Research article *Clinical research*

ISSN: 2521-2206

A comparative clinical study for the safety and efficacy of amlodipine besilate with telmisartan in patients suffering with essential hypertension

Anamika, M.Sampoorna, M.Ranadeep, M.Madhuri, N.Deepthi Reddy, N.Sahana

Department of Pharmacology, Teegala Ram Reddy College of Pharmacy, Meerpet, Hyderabad, Telangana, 500097.

***Address for correspondence: Dr. Anamika**

ABSTRACT

The use of multiple drug regimens is increasingly recognized as a tacit requirement for the management of hypertension, a necessity fueled in part by rising rates of metabolic syndrome and diabetes. By targeting complementary pathways, combinations of antihypertensive drugs can be applied to provide effective blood pressure control while minimizing side effects and reducing exposure to high doses of individual medications. In addition, combination therapies, including angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs), have the added benefit of reducing cardiovascular mortality and morbidity over other dual therapies while providing equivalent blood pressure control. It is possible that angiotensin receptor blockers (ARBs), which unlike ACE inhibitors are minimally affected by upregulation of alternative pathways for angiotensin II accumulation following long-term treatment, would also provide such outcome benefits. At issue, however, is maintaining patient compliance, as adding medications is known to reduce adherence to treatment regimens. The purpose of this review is to summarize existing trial data for the long-term safety and efficacy of a recent addition to the armamentarium of dual-antihypertensive therapeutic options, the telmisartan/amlodipine single pill combination. The areas where long-term data are lacking, notably clinical information regarding minorities and women, will also be discussed.

Keywords: Angiotensin receptor blocker, Antihypertensive, Calcium channel Blocker, Clinical trial, combination pill

INTRODUCTION

Hypertension is called the *"silent killer"* since it is often asymptomatic. It is also known as high blood pressure.The force of blood against the wall of arteries is known as blood pressure. High blood pressure can lead to many heart diseases and it also increases the risk of heart attacks and strokes.

Definition of hypertension

- Hypertension is defined as a blood pressure ≥ 140/90 mm Hg.
- Prehypertension refers to systolic blood pressure 120-139 mmHg or diastolic pressure of 80-89mmHg.
- Normal blood pressure is referred to as 120/80 mmHg.

Classification of hypertension

Hypertension is classified into four types. They are as follows [1]

Table.no.1 Classification of hypertension

Hypertension	Systolic Pressure	Diastolic Pressure
Stage 1 (mild)	140-159	90-99
Stage 2 (moderate)	160-179	100-109
Stage 3 (severe)	180-209	110-119
Stage 4 (very severe)	≥ 210	≥ 120

- Systolic pressure: It is peak pressure in the arteries, which occurs near the end of the cardiac cycle when the ventricles are contracting.
- Diastolic pressure: Diastolic pressure is minimum pressure in the arteries, which occurs near the beginning of the cardiac cycle when the ventricles are filled with blood.

Young diabetic patients should be considered hypertensive if there is a persistent elevation of BP greater than the 95th percentile for age.

Pathogenesis of hypertension is many times related to many factors that include excessive salt intake and genes. The type of blood pressure where exact cause cannot be pinpointed is known as essential hypertension (primary hypertension). The hereditary factor may be one of the reasons for this type of hypertension. It affects more men than women. Diet and lifestyle also play a role in pathophysiology. Overweight people often suffer from hypertension. Irregular sleep patterns also lead to hypertension. Hypertension is seen in people with excessive salt intake in their diet. These people are known as "salt sensitive." Their bodies exhibit high blood pressure, when the amount of salt in their blood is more than the body requirement. Low potassium and calcium intake, stress are also the causes of high pressure.

Secondary hypertension is the condition when one can pinpoint the exact cause of hypertension. Kidney diseases are the most common factor for secondary hypertension. Hypertension can also be caused by tumours of the adrenal glands. These tumours or abnormalities of the adrenal glands cause excessive secretion of hormones that led to hypertension. Oestrogen, the hormone found in birth control pills can also cause the blood pressure to elevate. Pregnancy is another factor that causes hypertension.

The development of arteriosclerosis and atherosclerosis are also affected by hypertension. Hypertension reduces the elasticity of arteries causing other secondary conditions which lead to decrease blood flow and ischemic diseases. Hypertension induced arteriosclerosis may lead to atrophy of renal glomeruli and tubules. This causes renal failure and may lead to death. Another serious complication arising due to hypertension is cerebrovascular diseases. Coronary diseases are the most common cause of death for hypertensive patients.

Hypertension should be diagnosed accurately, and it should be treated promptly in people with diabetes because they are at high risk for adverse CVD and renal outcomes. To avoid a potentially dangerous delay in diagnosis, it is reasonable confirm a diagnosis of hypertension in people with diabetes if the average blood pressure ≥ 130/80 mmHg on two successive visits scheduled within one month.

Blood pressure should be measured correctly. It can be measured directly or indirectly. There are four common devices used for the indirect measurement of BP namely:

Pharmacological therapy is initiated when life-style modifications fail to control hypertension (target BP < 130/80): for stage 1 and 2, after 2-3 month of lifestyle modifications; for stage 3 and 4, at the time of diagnosis. Further substitutions and additions should be based JNC_V recommendations until control is achieved. [102-103]

While all classes of antihypertensive drugs are equally effective in controlling blood pressure, six classes are effective for single agent therapy. [102]

Thiazide diuretics have been shown to benefit patients with diabetes and systolic hypertension. They control hypertension in part by inhibiting reabsorption of sodium (Na^+) and chloride (Cl^-)

ions from the distal convoluted tubules in the kidneys by blocking the thiazide-sensitive Na+Cl− symporter.

AIM AND OBJECTIVE

Aim

The aim of the study is to evaluate the safety and efficacy of fixed dose combination of amlodipine, telmisartan and hydrochlorthiazide in patients with hypertension.

Objective

- To evaluate the efficacy of the combination of drugs in subjects.
- To observe the adverse drug reactions and to record the adverse drug reactions.

MATERIALS AND METHODS

Study Design

This randomized, comparative, multicentre, 12 week, outpatient study evaluated antihypertensive efficacy of stelmisartan/ amlodipine/ hydrochlorthiazide combination in comparison with atenolol /amlodipine alone.

Study medication

Patients were selected into two groups.

- ✓ Fixed Dose Combination of telmisartan plus Amlodipine plus hydrochlorthiazide
- ✓ Fixed Dose Combination of Atenolol (25mg) plus Amlodipine (2.5 mg). The study drugs were administered orally once daily in morning.

Subjects: Patient selection

Willing to sign informed consent and ready for regular follow-up we enrolled in the study.

Inclusion criteria

Patients (either untreated or pre-treated with anti hypertensive agents) of either sex, aged 18 years and above, diagnosed of essential hypertension as per JNC 7 criteria.

EXCLUSION CRITERIA

- Patients with DBP >109 mmHg were excluded from the study.
- Patients with secondary hypertension, known history of hypersensitivity to study medication, patients with severe hypertension, significant medical illness, patients with electrolyte imbalance, abnormal hepatic, and renal functions were excluded from the trial.
- Pregnant and lactating women or females of childbearing potential not practicing contraception were excluded from the study.

Efficacy Evaluation

- Efficacy of the therapy in treated patients was evaluated by BP measurement a teach study visit throughout study period.
- Blood pressure was measured by auscultator method.
- Measurements were performed after 10 minutes rest in duplicate separated by 2 minutes and then average was taken.
- If the first 2 readings of DBP differed by more than 5 mmHg, additional reading was obtained and average o f 2 closest reading was taken.
- The study investigator at each site performed all the BP measurements through out the study period
- The same method was followed at all study sites for B P measurement.
- Patients were termed as responder if their BP was controlled (SBP, 140 mmHg and DBP < 90 mmHg).

Safety Evaluation

- All enrolled patients were evaluable for tolerability assessment.
- Safety evaluation was based on adverse events (AEs) reported during the study.
- AEs were categorized by the investigator based on their intensity as mild, moderate, or severe and the relationship to the study drug as none, probably not, possible, probable or definite.
- At every visit during the entire study period, the reported AEs, clinical state of patients and details of concomitant medications, if any were captured.

- Blood samples were obtained at baseline and at the end of 3 months therapy or at last follow-up visit for early termination/withdrawal cases to perform hematology and biochemistry tests including complete blood count urine routine, electrocardiogram, serum electrolytes (Na+2,Cl+,K), fasting blood glucose.

Statistical analysis

- The primary objective was to show that telmisartan/ amlodipine combination therapy is superior to atenolol/amlodipine combination therapy with respect to mean fall in SBP and DBP at the end of therapy from baseline. The sample size calculation required approximately 192 patients to be randomized and 174 evaluable patients (87 patients per treatment group) to complete the study to detect a treatment difference of at least 5 mmHg in the primary comparison with a power of 80% at 5% level of significance (2 sided).
- Descriptive statistics, including mean, SD, frequency counts and percentage for categorical variables were used to compare treatment groups at baseline with respect to demographic characteristics. The treatment groups were compared for homogeneity at baseline using tests like Student's t test, Mann–Whitney U test for continuous variables and chi-square test or Fisher's exact test for categorical variables.
- The 2 treatment groups were similar with respect to demographic characteristics. For data analysis, the whole population was divided into 2 subgroups, escalated patients and non escalated patients. None escalated patients included patients who received the baseline therapy up to 1 month and remained controlled on the same therapy to the end of study. While escalated patients include patients continued on the baseline therapy up to 1 month but escalate d to respective step-up therapies due to poor or no response to the baseline therapies. Both the treatment groups were compared after 1 month and the end of the study using Student's t test, Mann – Whitney U test as appropriate. All statistical tests we resided and the level of significance were set at 0.05. Statistic al analysis was performed using statistical software Graph Pad Prism Z6.01.

RESULTS

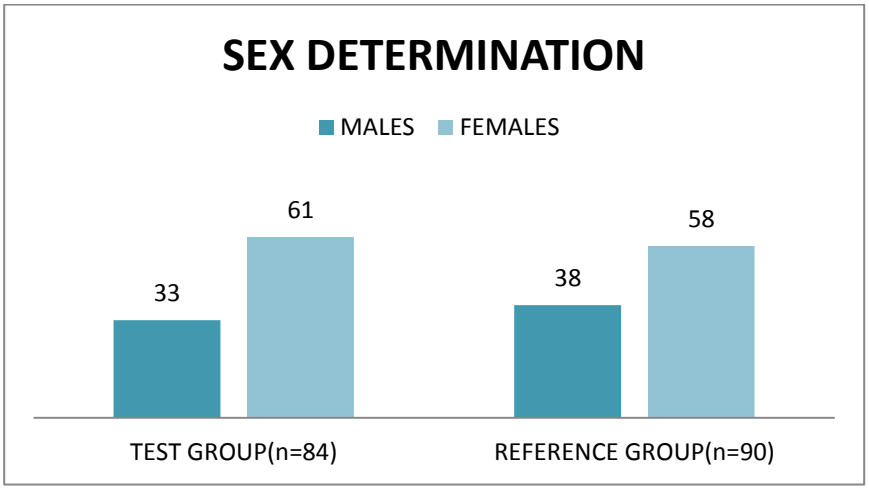
Patient distribution

- A total of 190 eligible patients (TEST GROUP: 94 subjects; COMPARATOR: 96 subjects) satisfying inclusion/exclusion criteria were enrolled on the study.
- Nine patients from test group and six patients from reference group were lost to follow-up
- 1 patient from test group was withdrawn due to adverse event.
- A total of 174 patients completed the study (test group: 84; reference group: 90). The 2 treatment groups were similar with respect to demography and baseline disease characteristics (Table 1).

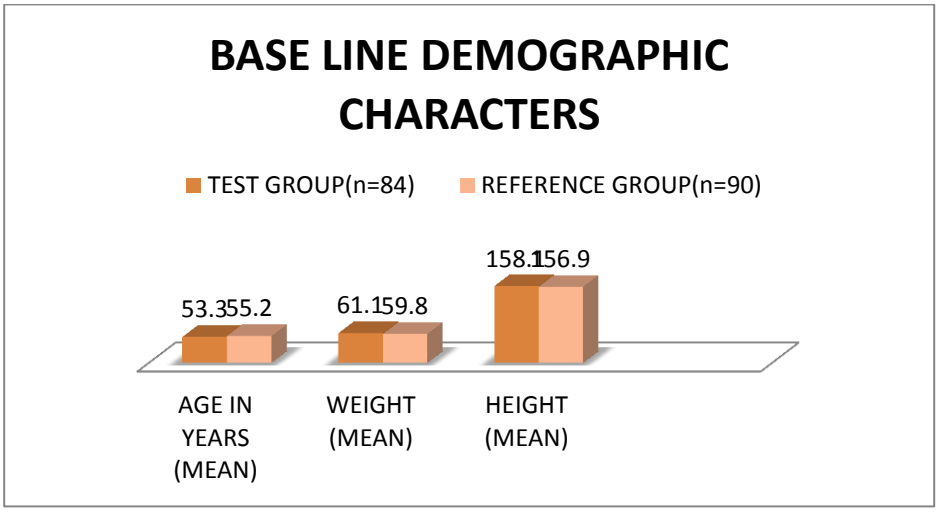
Table 1: Baseline characteristics of patients

Parameters	**Amlodipine/Telmisartan /hydrochlorthiazide (test group) (n=84)**	**Atenolol-amlodipine (n=90)**	***P* value**
Males (%)	33 (35.11)	38 (39.58)	0.524
Females (%)	61 (64.89)	58 (60.42)	-
Mean age (years) (range)	53.3 ±12.0 (25-80)	55.2±11.9(28-80)	0.274
Mean weight (kg) ±SD	61.1 ±10.8	59.8±10.7	0.395
Mean height (cm) ±SD	158.1 ±10.3	156.9±10.2	0.422
Heart rate (breaths/min) ±SD	79.62 ±7.54	79.46±6.86	0.880
Respiration rate (breaths/min) (mean± SD)	15.50± 2.96	15.49±2.53	0.979
Stage I essential hypertension	53	62	0.248
Stage II essential hypertension	41	34	-

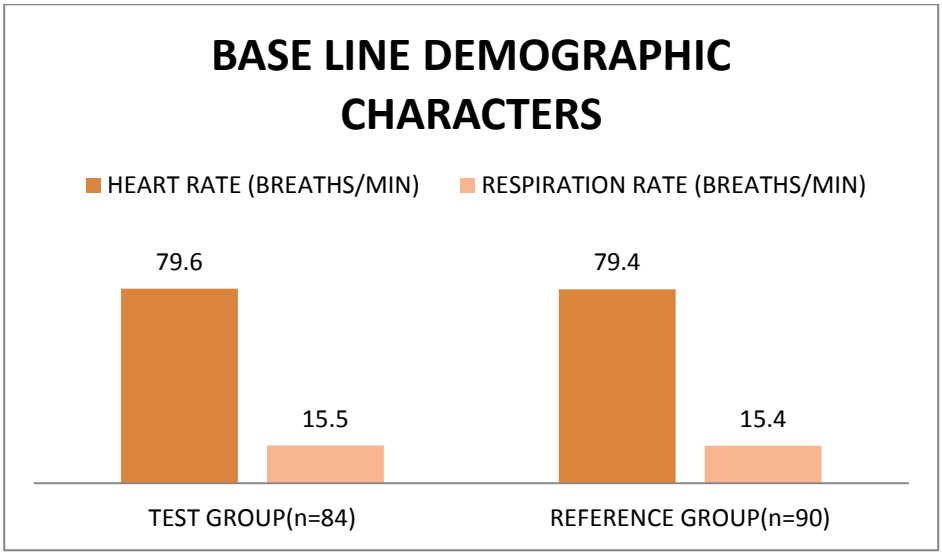
Systolic blood pressure (mmHg) (mean±SD)	156.17 ±9,82	153.1±11.6	0.051
Diastolic blood pressure (mmHg) (mean±SD)	95.06± 5.79	94.07±5.54	0.230



Graph No: 1-baseline demographic characteristic variables.gender.



Graph No: 2 - base line demographic variables age, height, weight.



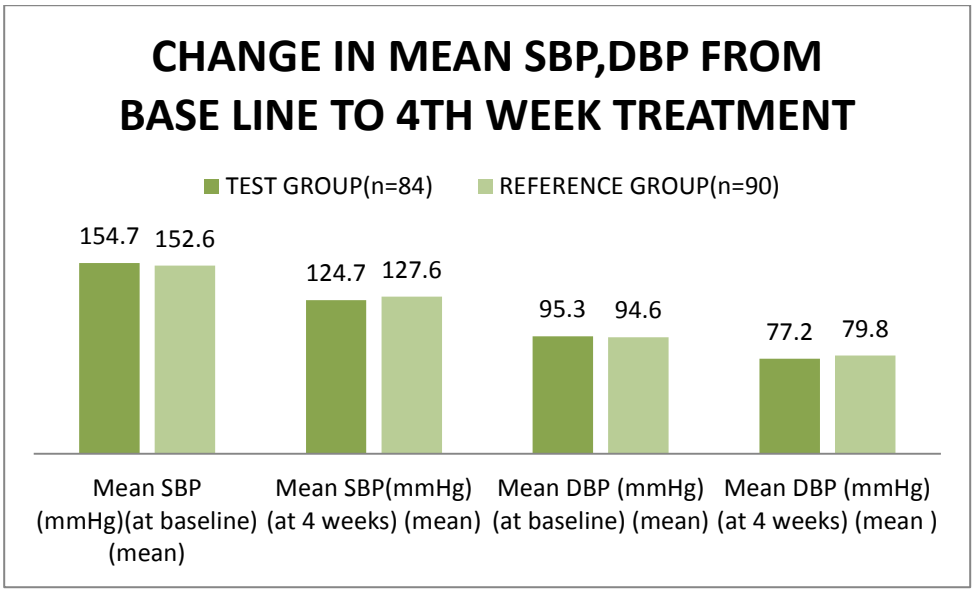
Graph No: 3- base line demographic characteristic variables heart rate, respiartory rate

Efficacy after 4 weeks of therapy

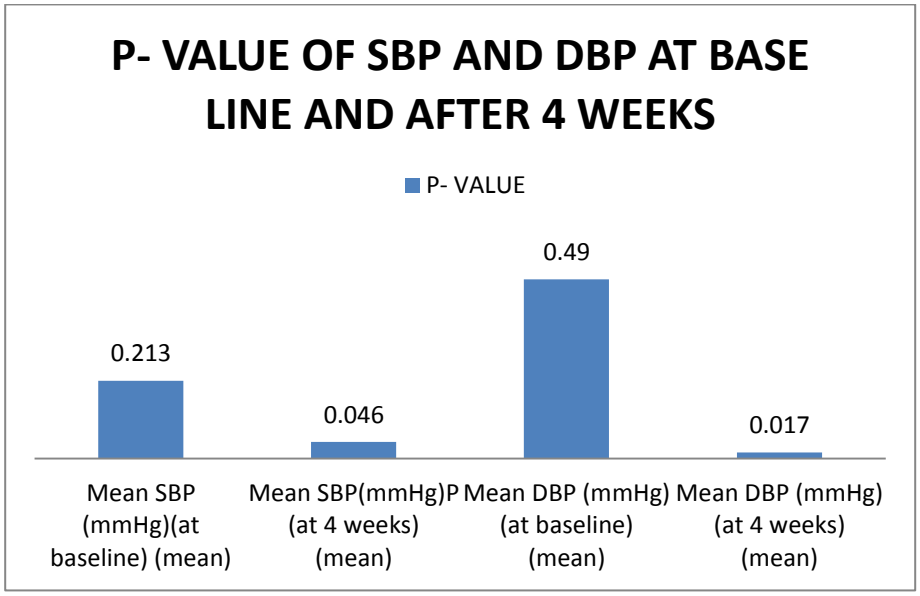
At the end of 4 weeks of therapy, 62 patients from test group and 50 patients from reference group responded to the therapy (SBP < 140 mmHg and DBP < 90 mmHg) (P = 0.012) (Table 2). Mean fall in SBP (-30 .0 ± 10.4 vs. -25.08 ± 9.05; P = 0.008) and DBP (-18 .10 ± 7.45 vs. -14.78 ± 7.48; P = 0.021) was significantly superior in test drug therapy as compared with reference drug combination therapy at the end of 4 weeks. Mean SBP and mean DBP was significantly lower in test drug combination group as compared with reference group at the end of 4 weeks of therapy (P < 0.05) (Table 2). Responders from both the treatment groups remained controlled till the end of therapy (day 90). Figure 1 show s fall in mean SBP and DBP for responders on starting therapies.

Table no2: Change in mean at base line and after 4 weeks.

Efficacy parameters	**TEST GROUP (n=62)**	**REFERENCE GROUP (n=50)**	***P* value**
Mean SBP (mmHg)(at baseline) (mean ±SD)	154.77±9.29	152.68±8.37	0.213
Mean SBP(mmHg)P (at 4 weeks) (mean ±SD)	124.74±6.76	127.60±7.97	0.046
Mean DBP (mmHg) (at baseline) (mean ±SD)	95.35±5.90	94.64±5.02	0.490
Mean DBP (mmHg) (at 4 weeks) (mean ±SD)	77.26±5.59	79.86±5.66	0.017
Mean DBP (mmHg) (at 4 weeks) (mean ±SD)	-30.0±10.4	-25.08±9.05	0.008
Mean fall in DBP (mmHg) (mean ±SD)	-18.10±7.45	-14.78±7.48	0.021



Graph no4: change in SBP snd DBP at baseline and after 4 weeks



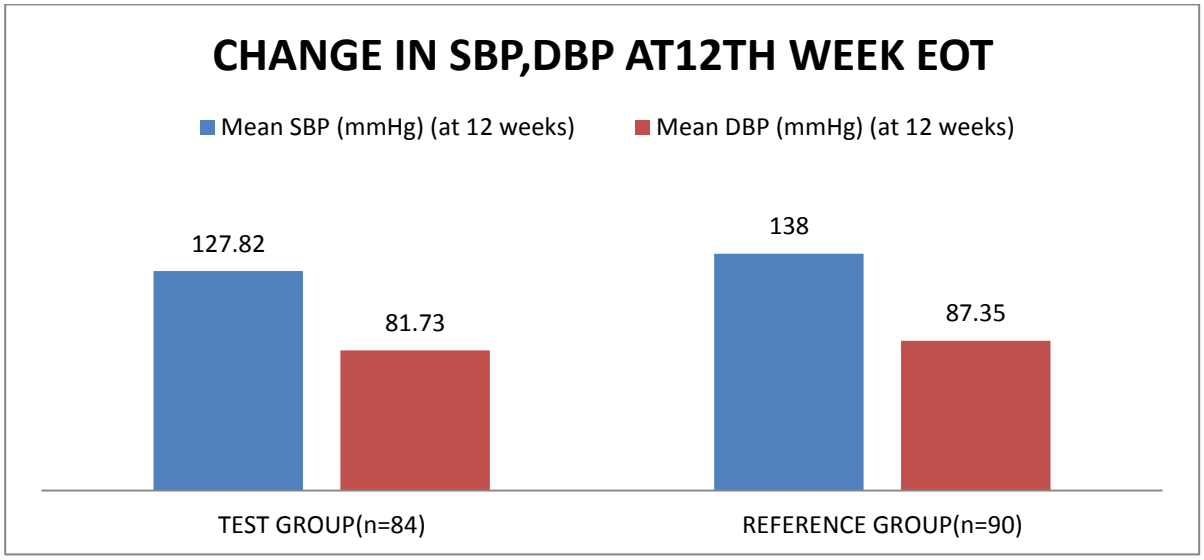
Graph no 5- p. value of: change in SBP and DBP at baseline and after 4 weeks

Efficacy after 12 weeks of therapy

- Sixty-two non responders (Ne/Am combination therapy:22; At/Am combination therapy:40) were escalated to respective step-up therapies to receive Nebivolol 5 mg/ Amlodipine 2.5 mg and atenolol 50 mg/ Amlodipine 2.5 mg for further 8 weeks. At the end of therapy, total 23 patients (Ne/Am combination therapy: 12; At/Am combination therapy group: 11) responded to the step-u p therapies (SBP < 140 mmHg and DBP < 90 mmHg). Step-up therapy of Ne/Am combination group showed significantly better response rate as compared with step-up therapy of atenolol/Amlodipine (P = 0.035) (Table 3).
- Both the step-up therapies were comparable with respect to mean fall in SBP and mean fall in DBP (P > 0.05) at the end of therapy. However, at the end of 12 weeks, mean SBP (127.82 ± 8.90 vs. 138.0 ± 14.4; P = 0.001) and mean DBP (81.73 ± 8.78 vs. 87.35 ± 5.50; P = 0.011) were significantly lower in Ne/Am combination group as compared with those in At/Am combination therapy group (Table 3). Nonresponders at the end of treatment period (10: Ne/Am combination group and 29: At/Am combination therapy group) were then treated appropriately at the discretion of the investigator.
- At the end of therapy, significantly more number of combination treated patients achieved normalization of BP (SBP < 120 mm Hg and DB P < 80 mmHg) as compared with At/Am combination therapy (33 vs. 19) (P = 0.009). In both the treatment groups, the fall in BP was maximum at the end of 4 weeks of therapy, and subsequently the fall was maintained till the end of therapy, that is, day 90 (Figure 2).

Table no 3- change in SBP and DBP after 12 weeks of treatment

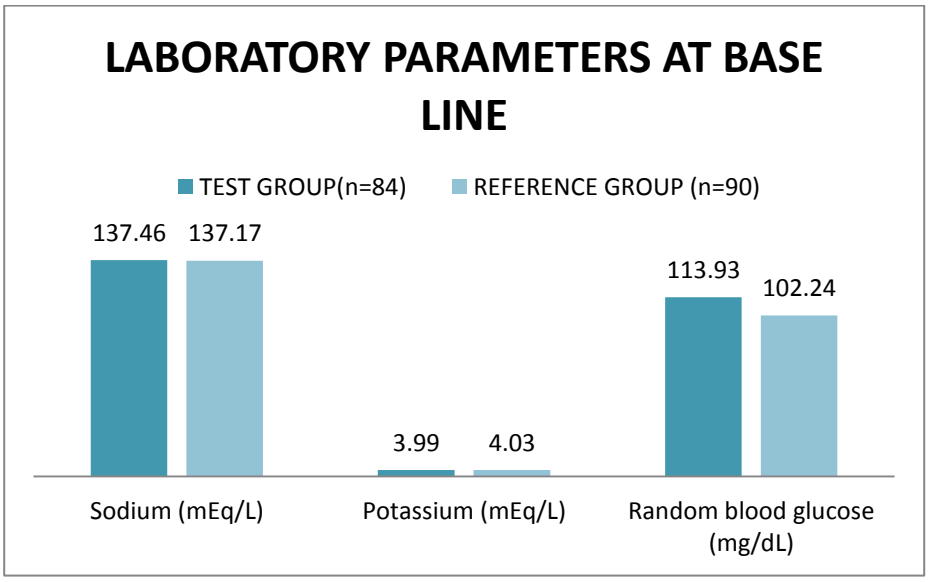
Efficacy parameters	**TEST GROUP (n=84)**	**REFERENCE GROUP (n=90)**	***P* value**
Mean SBP (mmHg) (at 12 weeks)	127.82 ±8.90	138.0 ±14.4	0.001
Mean DBP (mmHg) (at 12 weeks)	81.73 ±8.78	87.35 ±5.50	0.011



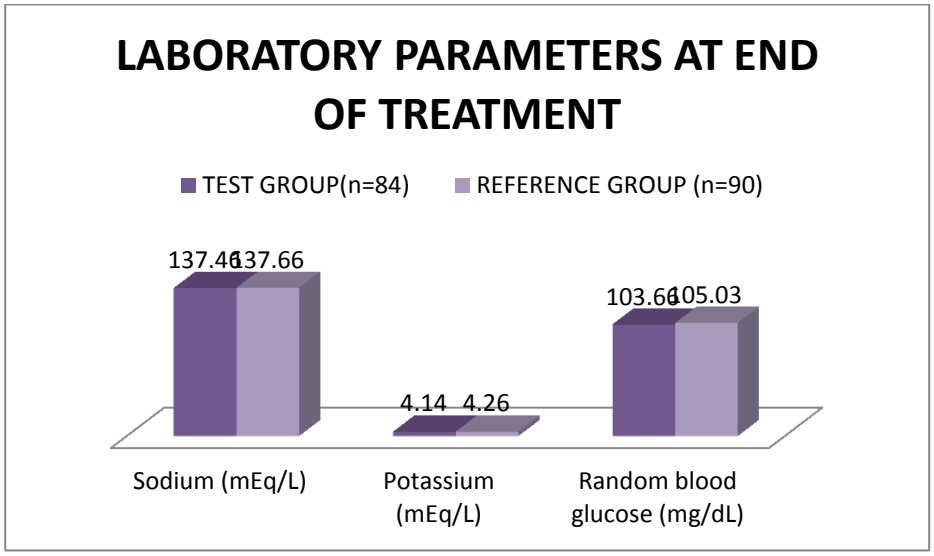
Graph No: 6- Change in Sbp and Dbp after 12 weeks of treatment

Table no 4: laboratory parameters

Laboratory parameters	**Visit**	**TEST GROUP(n=84)**	**REFERENCE GROUP (n=90)**	***P* value**
Sodium (mEq/L)	Baseline	137.46 ±5.03	137.17 ±4.63	0.619
	End	137.46 ±5.40	137.66 ±5.40	
	P value	1.0	0.441	
Potassium (mEq/L)	Baseline	3.99± 0.68	4.03± 0.72	0.600
	End	4.14 ±0.56	4.26 ±0.54	
	P value	0.129	0.025	
Random blood glucose (mg/dL)	Baseline	113.93 ±47.54	102.24 ±23.59	0.245
	End	103.66 ±48.99	105.03 ±29.51	
	P value	0.328	0.480	



Graph no 7: laboratory parameters.



Tolerability assessment

- A total of 4 patients reported adverse events, 3 from combination therapy and 1 from monotherapy.
- Edema, gastritis, and abdominal pain were reported in patients treated with combination therapy and giddiness was reported in patients treated with monotherapy.
- All reported adverse events were of mild-to - moderate in severity. None of the patients reported serious adverse event.
- The laboratory evaluations were done at baseline and at the end of therapy.
- Mean change s from baseline for various laboratory parameters were evaluated at the end of 3 months for all patients.
- There was non-significant reduction in heart rate at the end of therapy with either treatment.
- No significant changes from baseline were observed in haematology or biochemistry parameters
- Changes in blood glucose levels and lipid profile (high-density lipoprotein, low-density lipoprotein, triglycerides, and total cholesterol) were clinically unremarkable across the therapy groups.

Safety Assessment

Side effects found with Atenolol-amlodipine combinations

- Tiredness -- in up to 26 percent of people
- Low blood pressure (hypotension) -- up to 25 percent
- Slow heart rate (bradycardia) -- up to 18 percent
- Dizziness -- up to 13 percent
- Cold hands or feet -- up to 12 percent
- Depression -- up to 12 percent *(see Atenolol and Depression*
- Shortness of breath -- up to 6 percent
- Fatigue -- up to 6 percent.

Other common side effects of atenolol (occurring in 2 to 4 percent of people) include but are not limited to

- Leg pain
- A decrease in blood pressure when going from a lying-down or sitting position to standing
- A spinning sensation (vertigo)
- Lightheadedness
- Diarrhea
- Nausea

SIDE EFFECTS FOUND WITH Investigational product

- Headache -- in up to 9 percent of people
- Fatigue -- up to 5 percent
- Dizziness -- up to 4 percent
- Diarrhea -- up to 3 percent
- Nausea -- up to 3 percent
- Insomnia -- up to 1 percent.

DISCUSSION

- The primary goal of treating hypertension is to reduce their blood pressure to target level, which eventually leads to a reduction in the long-term total risk of cardiovascular morbidity and mortality.
- In this regard, although some considerations are necessary before generalizing the results, the present study clearly demonstrated that combination therapy with aangiotensin receptor blocker and a calcium channel blocker is an effective method to achieve the target blood pressure without major safety issues.
- This randomized, comparative, multicentre, 12 week, outpatient study evaluated antihypertensive efficacy of telmisartan/ amlodipine besylatecombination in comparison with atenolol /amlodipine alone.
- The results of this study showed that, telmisartan/amlodipine/hydrochlorthiazide combination therapy with is superior to atenolol/amlodipine combination therapy with respect to mean fall in SBP, DBP, response rate, and normalization of BP.
- After 4 weeks of therapy with reference drug, our study reported a fall of -20.6/ -10.34 in SBP/DBP which is com parable to that reported in literature (-17.6/ -12.5). In our study, for responders after4 weeks of therapy, low-dose combination of INVESTIGATIONAL PRODUCT was found to be superior to low-dose atenolol 25 mg/Amlodipine 2.5mg combination therapy with respect to mean fall in SBP (P = 0.008), mean fall in DBP (P = 0.021) and response rate (P = 0.012).One reason for combining a calcium antagonist with a angiotensin receptor blockerin the treatment of mild to-moderate hypertension is that the latter should improve the patient tolerability of the former by preventing any initial reflex tachycardia which may, in it, because of some adverse effects.
- The results of our study confirmed that the combination therapy with telmisartan/amlodipine/hydrochlorthiazide is superior to atenolol/Amlodipine combination therapy in patients with mild-to-moderate essential hypertension.

CONCLUSION

The study was conducted in OM SAI HOSPITALS, HYDERABAD for a period of 12 weeks. The efficacy and safety was studied on the finished population. In conclusion, our study has shown that once daily treatment with telmisartan offered superior antihypertensive efficacy over Amlodipine combination therapy in patients with mild-to-moderate essential hypertension.

REFERENCE

[1]. Lima.M, Mendez V, Perez W. Gross anatomy of heart in the western grey kangaroo.Int.J.Morphol. 27(4), 2009, 1099.
[2]. http://www.biologyabout.com/od/humananatomybiology/ss/heart_anatomy.htm Retrived on 25/6/2012.
[3]. Calder AL, Co EE, Sage MD. Coronary arterial abnormalities in pulmonary atresia with intact ventricular septum. Am J Cardiol 59, 1987, 436–42.
[4]. Burrows PE, Freedom RM, Benson LN, Moes CA, Wilson G, Koike K, Williams WG. Coronary angiography of pulmonary atresia, hypoplastic right ventricle, and ventriculocoronary communications. Am J Roentgenol 154, 1990, 789–95.
[5]. Pasquini L, Sanders SP, Parness IA, Wernovsky G, Mayer JE Jr, Van der Velde ME, et al. Coronary echocardiography in 406 patients with d-loop transposition of the great arteries. J Am CollCardiol 24, 1994, 763–8.
[6]. Hanley FL, Sade RM, Blackstone EH, Kirklin JW, Freedom RM, Nanda NC. Outcomes in neonatal pulmonary atresia with intact ventricular septum. A multiinstitutional study. J ThoracCardiovascSurg 105, 1993, 406–27.
[7]. Jatene AD, Fontes VF, Paulista PP, Souza LC, Neger F, Galantier M, Sousa JE. Anatomic correction of transposition of the great vessels. J ThoracCardiovascSurg 72, 1976, 364–70.

[8]. Gittenberger-de Groot AC, Sauer U, Oppenheimer-Decker A, Quaegebeur J. Coronary arterial anatomy in transposition of the great arteries: a morphologic study. PediatrCardiol 4, 1983, 15–24.
[9]. VranckenPeeters MP, Gittenberger-de Groot AC, Mentink MM, Hungerford JE, Little CD, Poelmann RE. The development of the coronary vessels and their differentiation into arteries and veins in the embryonic quail heart. DevDyn 208, 1997, 338–48.
[10]. McKay R, Anderson RH, Smith A. The coronary arteries in hearts with discordant atrioventricular connections. J ThoracCardiovascSurg 111, 1996, 988–97.
[11]. www.pfizerindia.com/health_hy.html retrived on 12/5/2012.
[12]. www.wrongdiagnosis.com/h/hypertension/symptoms.html
[13]. www.diethealthclub.com/health-issues-and-diet/hypertension.html
[14]. www.webmd.com/hypertension-high-blood-pressure/tc/high-blood-pressure-hypertension-symptoms.html
[15]. http://www.mco.edu/org/whl/bloodpre.html. Accessed April 1, 2003.
[16]. http://www.americanheart.org/presenter.jhtml?identifier=576. Accessed April 1, 2003.
[17]. http://www.nhlbi.nih.gov/about/nhbpep/index.htm. Accessed March 5, 2003.
[18]. Promising.Y, Nelson MR, McNeil JJ, Peeters A et al. "PBS/RPBS cost implications of trends and guideline recommendations in the pharmacological management of hypertension in Australia, 1994-1998". Med J Aust Jun 4 174(11), 2001, 565–8