

A STUDY ON THE SAFETY AND EFFICACY PROFILE OF AMLODIPINE BESILATE COMPARED WITH OLMESARTAN IN HYPERTENSION PATIENTS

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ABSTRACT: People over 62, those with a body mass index of 30 kg/m², Black people, and people with type II diabetes are more likely to have high blood pressure. We present a planned secondary study of how well amlodipine (2.5 mg/day), Olmesartan (20 mg/day), a mix of the two, and a sugar pill worked in these subgroups. The study was conducted in PRIME HOSPITALS, HYDERABAD for a period of 12 weeks. The results of this study showed that amlodipine besylate combination therapy with is superior to Olmesartan therapy with respect to mean fall in SBP, DBP, response rate, and normalization of BP. After 4 weeks of therapy with atenolol 25mg, our study reported a fall of -20.6/ -10.34 in SBP/DBP which is comparable to that reported in the literature (-17.6/-12.5). In our study, for responders after 4 weeks of therapy, a low dose of INVESTIGATIONAL PRODUCT was found to be superior to low-dose reference drug therapy with respect to mean fall in SBP (P=0.008), mean fall in DBP (P=0.021) and response rate (P=0.012). The results of our study confirmed that the combination therapy with amlodipine besylate is superior to Olmesartan therapy in patients with mild-to-moderate essential hypertension.

I. 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 of 140/90 mmHg.
- Prehypertension refers to systolic blood pressure of 120-139 mmHg or diastolic pressure of 80-89 mmHg.
- 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.I 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 the 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 95 percentile for age.

II. PURPOSE OF THE STUDY

Essential hypertension remains a major modifiable risk factor for cardiovascular disease (CVD) despite important advances in our understanding of its pathophysiology and the availability of effective treatment strategies. High blood pressure (BP) increases the risk of CVD for millions of people worldwide, and there is evidence that the problem is only getting worse. Essential hypertension can begin at any age. It most often occurs first during the middle-age years. Single drug-antihypertensive therapy is unsuccessful in up to half of all patients with hypertension. Hypertension control remains problematic, and they are frequently difficult to apply in everyday clinical practice.

The goal of this study is to study the safety and efficacy of amlodipine besylate in essential hypertension.

To compare the antihypertensive effect and tolerability of amlodipine besylate with Olmesartan in essential hypertension.

The primary objective of this study is to evaluate the safety of long-term administration of amlodipine besylate in patients with essential hypertension.

To assess the effects of the investigational drug X and the reference drug on standing blood pressure, sitting pulse, and standing pulse.

Drug Profile:

Amlodipine:

Class: Dihydropyridines

Chemical Name: RS)-3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate

Molecular Formula: $C_{20}H_{25}ClN_2O_5$

Structure:

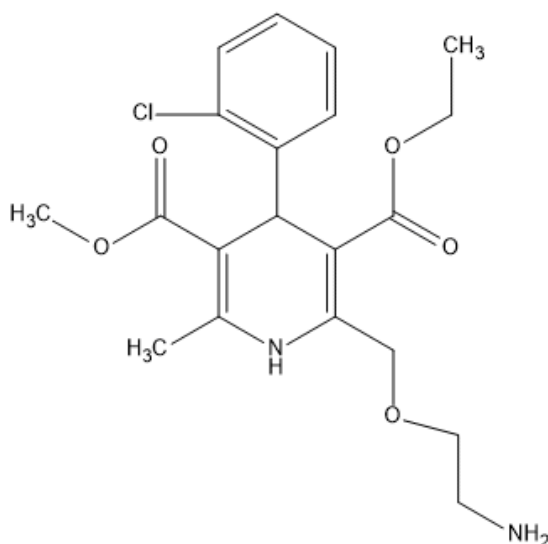


Fig.1. Brands: Azor (Combination), Caduet, Exforge (combination), Lotrel, Norvasc

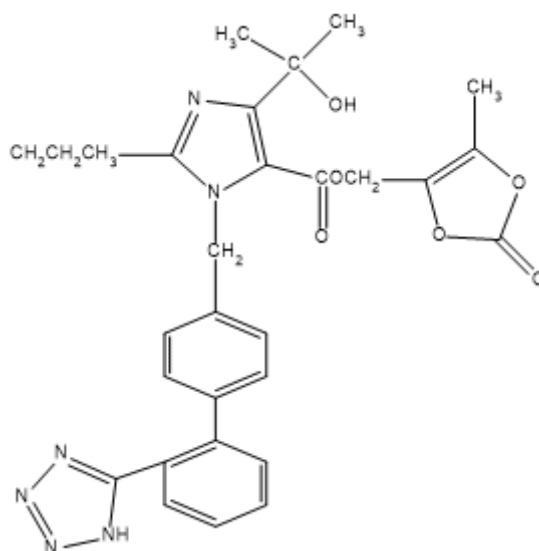
Olmesartan

Olmesartan is an antihypertensive agent, that belongs to the class of medications called angiotensin II receptor blockers. It is indicated for the treatment of high blood pressure and is marketed under the name Olmetec®. The FDA label includes a black-box warning of injury and death to the fetus, so women of childbearing age are contraindicated in diabetes mellitus patients taking Aliskiren.

IUPAC: 4-(2-hydroxypropan-2-yl)-2-propyl-1-((4-[2-(1H-1,2,3,4-tetrazol-5-yl)phenyl]methyl)-1H-imidazole-5-carboxylic acid

CHEMICAL FORMULA: $C_{24}H_{26}N_6O_3$

structure:



Average:446.5016

Monoisotopic:446.206638728

This compound belongs to the class of organic compounds known as biphenylterazole and derivatives. These are organic compounds containing a biphenyl attached to tetrazole. A carbon atom of the biphenyl is attached to a tetrazole. A carbon atom of the biphenyl moiety is bonded to carbon or the nitrogen atom of the tetrazole moiety. It is used for the treatment of hypertension.

III. MATERIALS AND METHODS

This randomized, comparative, multicentre, 12-week, outpatient study evaluated the antihypertensive efficacy of amlodipine besylate combination in comparison with Olmesartan alone.

Patients were selected into two groups.

Fixed-Dose Combination of Amlodipine besylate (2.5mg)

Fixed-Dose Combination of Olmesartan (20mg)

The study drugs were administered orally once daily in the 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 with 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, and 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.

Ethics Committee:

- The study was approved by the independent ethics committee of each centre.
- All Patients were provided an oral explanation about the nature of the study and about study drugs by the investigator at each center.
- An information sheet was provided in a language understood by the patient, and written informed consent was obtained from each participant before any study-related procedure.
- The execution and monitoring of the study were done in accordance with the requirements of good clinical practice.

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 least 5mmHg in the primary comparison with a POWER OF 80% at 5% level of significance (2sided).

- 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, 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 up to 1 month and remained controlled on the same therapy to end of study. While-escalated patients include patients continued on the baseline therapy up to 1 month but escalated 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 were used and the level of significance was set at 0.05. Statistical analysis was performed using statistical software Graph pad prism Z6.01.

IV. RESULTS

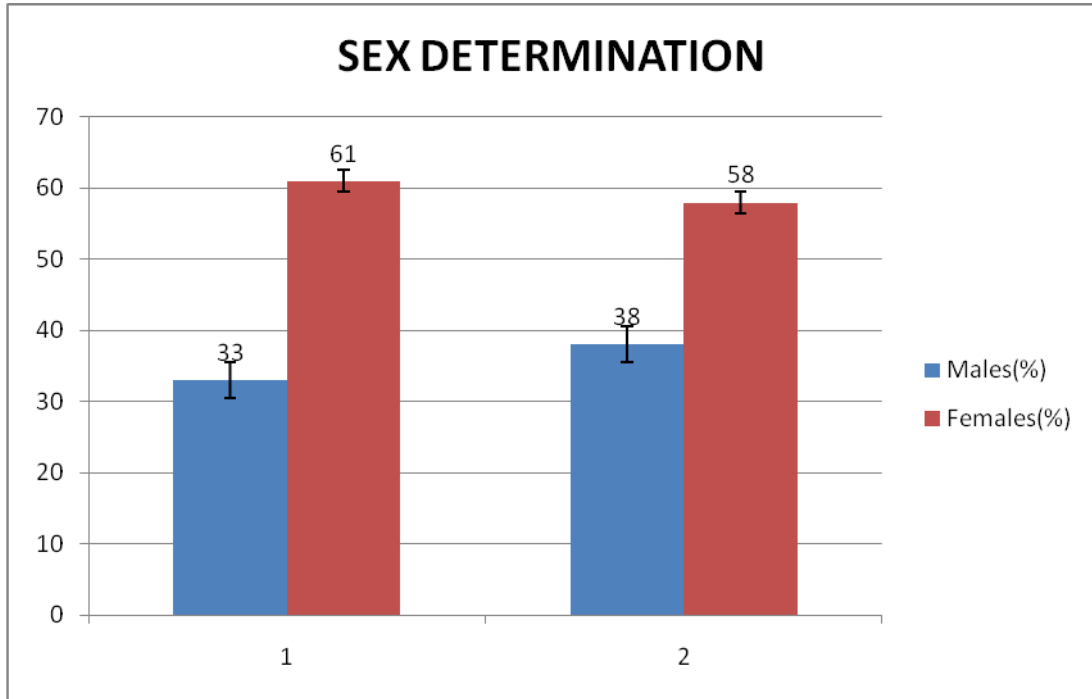
Patient distribution:

- A total of 190 eligible patients (TEST group: 94 subjects; COMPARATOR subjects) satisfying inclusion/exclusion criteria were enrolled on the study.
- Nine patients from test group and six patients from the 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 groups were similar with respect to demography and baseline disease characteristics (Table 1).

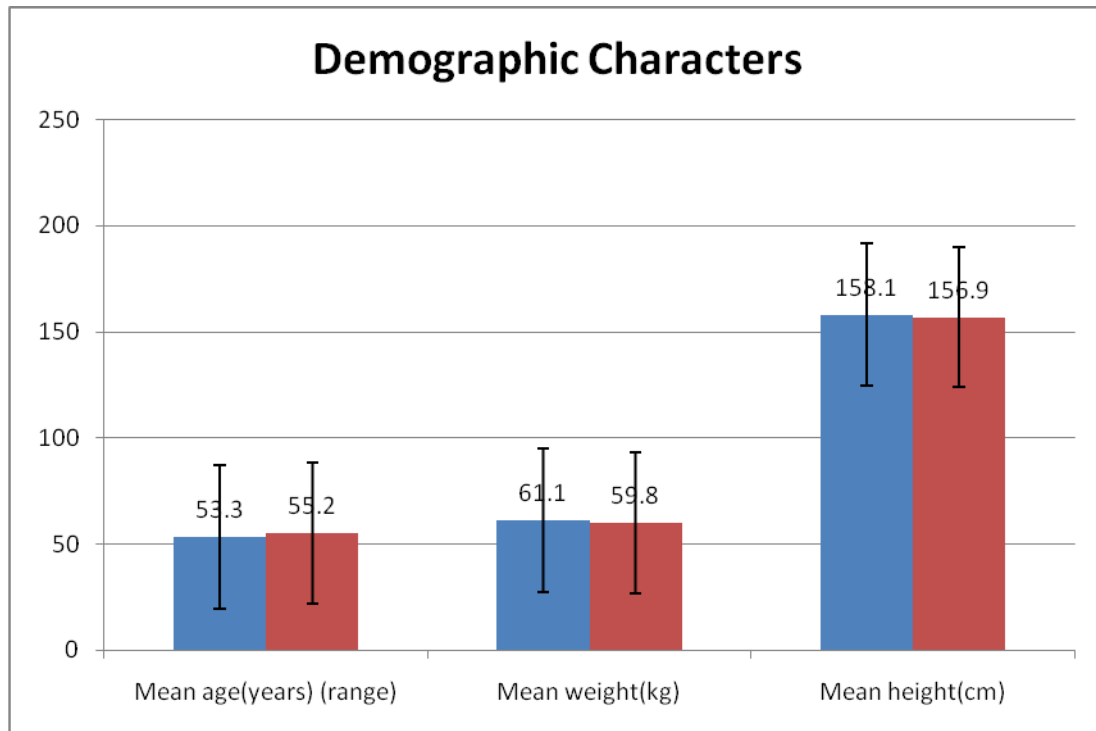
Table-1: Baseline characteristics of patients

Parameters	Amlodipine besylate (test group) (n=84)	Olmesartan(n=90)	P Value
Males (%)	33(35.11)	38(39.58)	0.524
Females (%)	61(64.89)	58(60.42)	-
Mean age(years) (range)	53.03±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±11.6	0.051
Diastolic blood pressure(mmHg)(mean±SD)	95.06±5.79	94.07±5.54	0.230

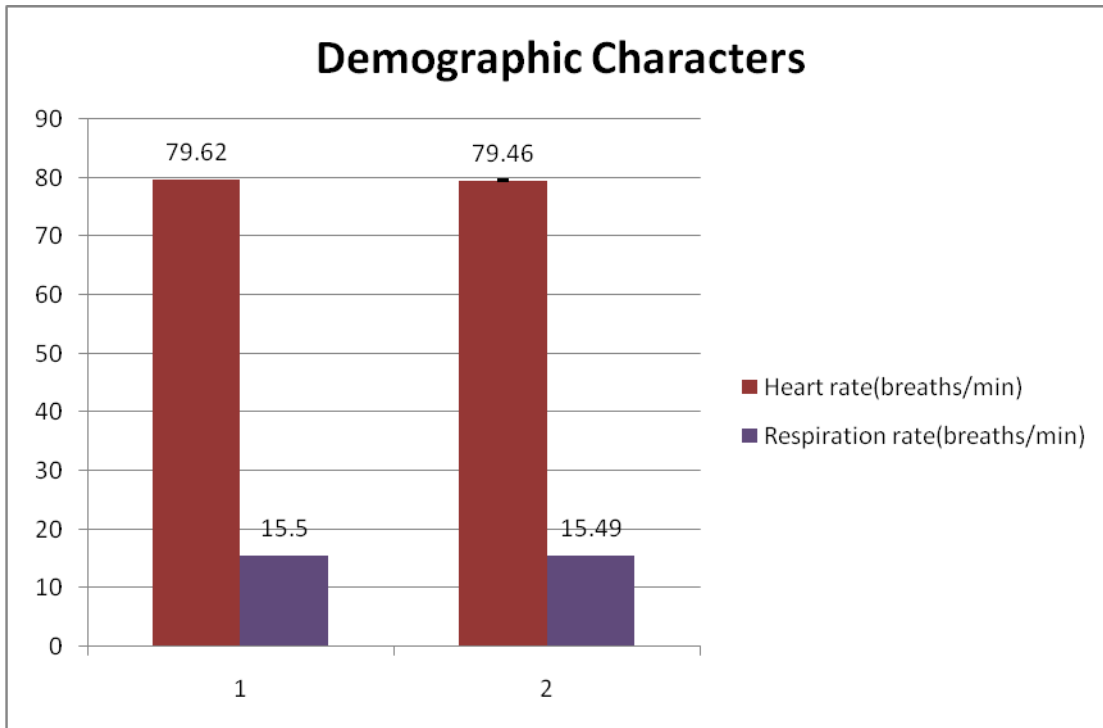
Graph No:1- Baseline demographic characteristic variables gender.



Graph no:2-Base linedemographic variables Age, Height, Weight.



Graph:3-Demographic Characteristic Variables Heart Rate, Respiratory Rate

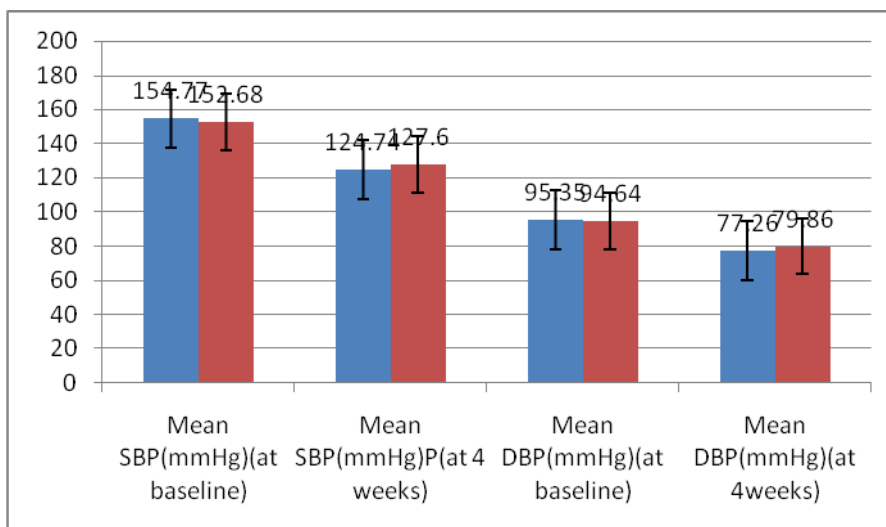
**Efficacy after 4 weeks of therapy:**

At the end of 4 weeks of therapy, 62 patients from the test group and 50 patients from the reference group responded to the therapy (SBP < 140 mmHg and DBP < 90 mmHg) ($P=0.012$) (Table 2). Mean responded to the therapy (SBP, 140 mmHg, and DBP $(-18.10 \pm 7.45$ 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 were significantly lower in test drug group as compared with the reference group at the end of 4 weeks of therapy ($P < 0.05$) (Table 2). Responders from both treatment groups remained controlled till the end of therapy (day 90). Figure I shows a fall in mean SBP and DBP for responders on starting therapies.

Table No-2: Change In Mean At Baseline And After 4 Weeks.

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

Graph no 4 :Change In SBP SND DBP At Baseline and After 4 weeks



Efficacy after 12 weeks of therapy

- Sixty-two nonresponders (Ne/Am combination therapy:22; At/Am combination therapy:40)were escalatedto respective step-up therapy:22;At/Am combination therapy:40)were escalated to respective step-up therapies to receiveNebivolol 5mg/Amlodipine 2.5mg for further 8weeks.At the end of therapy, total 23 patients(test drug therapy:12;olmesartantherapy group:11)responded to the step-u p therapies(SBP<140 mm Hg and DBP<90mmHg).Step-up therapy of test group showed significantly better response rate as compared with step-up therapy of Olmesartan(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 12weeks, mean SBP(127.82±8.78vs.87.35±5.50; P=0.011)were significantly lower in test group therapy(Table 3).Nonresponses at the end of treatment period(10:test group and 29:olmesartan 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<120mm Hg and DB P<80mm Hg)as compared with Olmesartan 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 falls was maintained till the end of therapy, that is, 90(Figure 2).

Table No 3-Change inSBP And DBP After 12 Weeks Of Treatment

Efficacy parameters	TEST GROUP(n=84)	REFERENCE GROUP (n=90)	P Value
Mean SBP(mm Hg)(at 12 weeks)	127.82±14.4	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 weeksof Treatment

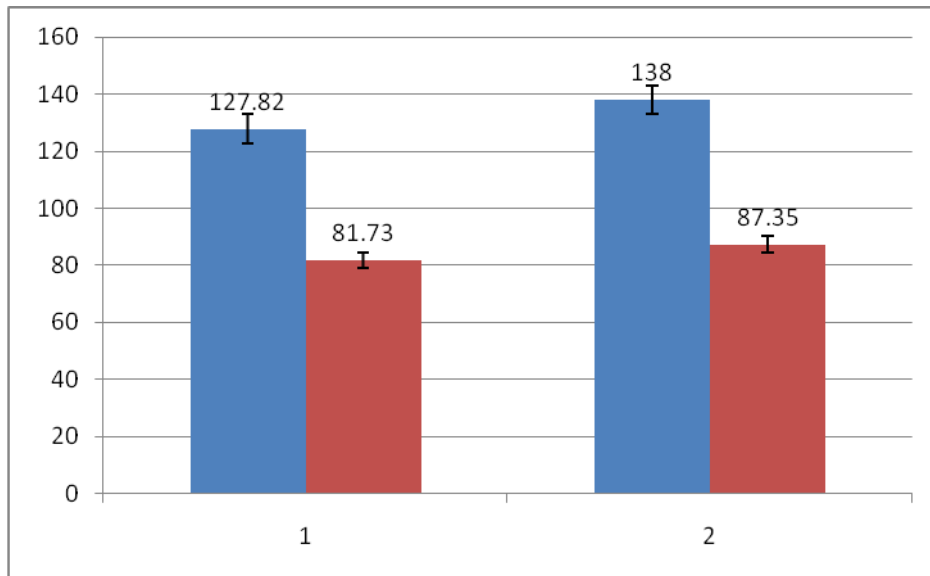
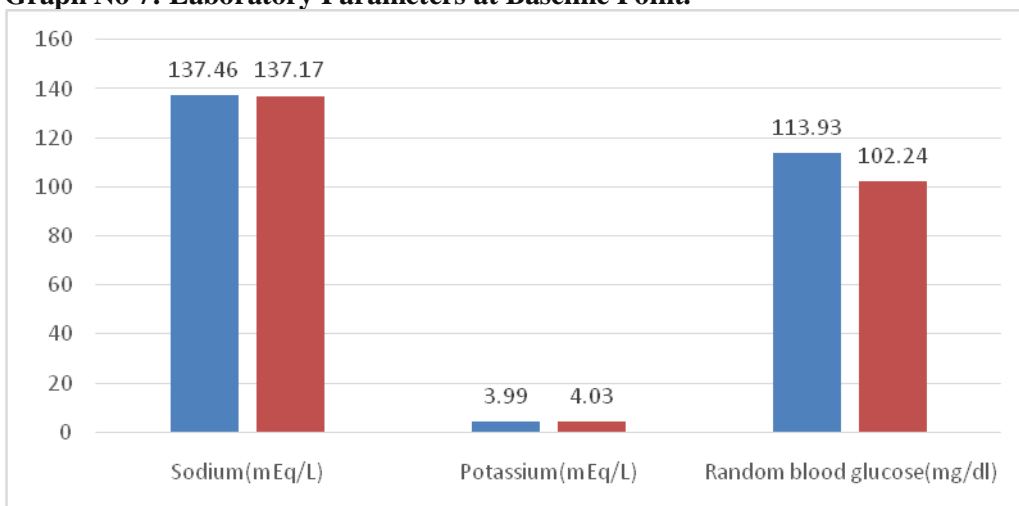
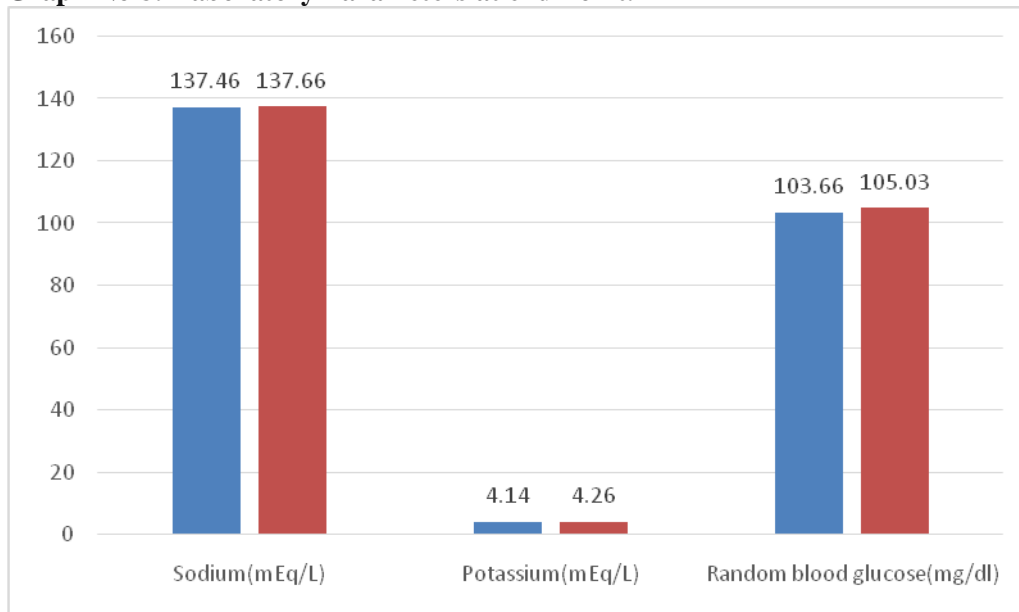


Table no 4: laboratory parameters.

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 ±0.072	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 at Baseline Point.



Graph No 8: Laboratory Parameters at end Point.**Tolerability assessment:**

- A total of 4 patients reported adverse events. Edema, gastritis, and abdominal pain were reported in patients treated;
- All reported adverse events were mild-to-moderate in severity. None of the Patients reported serious adverse events.
- The laboratory evaluations were done at baseline and at the end of therapy.
- Mean changes from baseline for various laboratory parameters were evaluated at the end of 3 months for all patients.
- There was no 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 Olmesartan

- 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 Shortness of breath—up to 6 percent
- Fatigue -up to 6 percent.

Side effects found with INVESTIGATIONAL PRODUCT-

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

V. DISCUSSION

- The primary goal of treating hypertension is to reduce blood pressure to the 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 demonstrated that test drug therapy is an effective method to achieve the target blood pressure without major safety issues.

- This randomized, comparative, multicentre, 12-week, outpatient study evaluated the antihypertensive efficacy of amlodipine besylate combination in comparison with Olmesartan alone.
- The results of this study showed that amlodipine besylate combination therapy with is superior to Olmesartan therapy with respect to mean fall in SBP, DBP, response rate, and normalization of BP.
- After 4 weeks of therapy with atenolol 25mg, our study reported a fall of -20.6/ -10.34 in SBP/DBP which is comparable to that reported in the literature (-17.6/-12.5). In our study, for responders after 4 weeks of therapy, a low dose of INVESTIGATIONAL PRODUCT was found to be superior to low-dose reference drug 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 an angiotensin receptor blocker in 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 amlodipine besylate is superior to Olmesartan therapy in patients with mild-to-moderate essential hypertension.

VI. CONCLUSION

The study was conducted in PRIME HOSPITALS, HYDERABAD for a period of 12 weeks. The efficacy and safety were studied in the finished population. In conclusion, our study has shown that once-daily treatment with amlodipine besylate offers superior antihypertensive efficacy over Olmesartan therapy in patients with mild-to-moderate essential hypertension.

REFERENCES

- [1] Lima. M, Mendea V, Perez w. Gross anatomy of heart in the western grey kangaroo. *Int. J. Morphol.* Dec 2009; 27(4): 1099-104. <http://www.health.am/cardio/more/anatomy-of-the-heart.html> retrieved on 12/5/2012.
- [2] <http://www.health.am/cardio/more/anatomy-of-the-heart.html> retrieved on 25/6/2012.
- [3] http://www.biologyabout.com/od/humanatomybiology/ss/heart_anatomy.htm Retrieved on 25/6/2012.
- [4] Calder AL, Co EE, Sage MD. Coronary arterial abnormalities in pulmonary atresia with intact ventricular septum. *Am J Cardiol* 1987; 59: 436-42.
- [5] Burrows PE, Freedom RM, Benson LN, Moes CA, Wilson G, Koike K, Williams WG. Coronary echocardiography in pulmonary atresia, hypoplastic right ventricle, and ventriculocoronary communications. *Am J ROENTGENOL* 1990; 154: 789-95.
- [6] Pasquini L, Sanders SP, Parness IA, Wernovsky G, Mayer JE Jr, Vander Velde ME, et al. Coronary echocardiography in 496 patients with d-loop transposition of the great arteries. *J Am Coll Cardiol* 1994; 24: 763-8.
- [7] Hanley FL, Sade RM, Blackstone EH, Kirklin JW, Freedom RM, Nanda NC. Outcomes in neonatal pulmonary atresia with intact ventricular septum. A multi institutional study. *J Thorac Cardiovasc Surg* 1993; 105: 406-27.
- [8] Jatene AD, Fontes VF, Paaulista PP, Souza LC, Neger F, Galantier M, Sousa JE. Anatomic correction of transposition of the great vessels. *J Thorac Cardiovasc Surg* 1976; 72: 364-70.
- [9] Gittenberger-de Groot AC, Sauer U, Oppenheimer-Deceker A, Quaegebeur J. Coronary arterial anatomy in transposition of the great arteries: a morphologic study. *Pediatr Cardiol* 1983; 4(Suppl 1): 15-24.
- [10] Vrancken Peeters MP, Gittenberger-de Groot AC, Mentink MM, Hugerford JEL, Little CD, Poelmann RE. The development of the coronary vessels and their differentiation into arteries and veins in the embryonic quail heart. *Dev Dyn* 1997; 208: 337-48.
- [11] McKay R, Anderson RH, Smith A. The coronary arteries in hearts with discordant atrioventricular connections. *Thora Cardiovasc Surg* 1996; 111: 1988-97.
- [12] www.pfizerindia.com/health_hy.html RETRIVED ON 12/5/2012.
- [13] www.wrongdiagnosis.com/h/hypertension/symptoms.html.