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EVALUATION OF SAFETY AND EFFICACY OF FIXED DOSE COMBINATION OF TELMISARTAN 20mg AND AMLODIPINE BESYLATE WITH ATENOLOL/AMLODIPINE COBMINATION FOR THE TREATMENT OF ESSENTIAL HYPERTENSION

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ABSTRACT

Objective: To evaluate the efficacy and safety of the telmisartan plus amlodipine (T/A) single-pill combination (SPC) in Asian patients with hypertension whose blood pressure (BP) was not adequately controlled on either monotherapy or on low-dose combination therapy. Patients and **Methods:** 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patients from test group and six patients from reference group were lost to follow-up. 1 patient from test group was withdrawn due to adverse event.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. Results: 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). 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. Discussion and Conclusion: 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.

KEYWORDS: Hypertension; Diabetes; Telmesartan; Amlodipine; Angina; Tachyarrhythmias.

INTRODUCTION

1) HYPERTENSION

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.

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

There are two types of blood pressure. Systolic pressure is peak pressure in the arteries, which occurs near the end of the cardiac cycle when the ventricles are contracting while 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.

2) CAUSES OF HYPERTENSION

There are two types of blood pressure. They are:

Primary (Essential) hypertension

Secondary hypertension

3) CAUSES OF HYPERYENSION

a) Renal artery stenosis (renovascular disease)

b) Chronic renal failure

c) Primary hyperaldosteronism

d) Stress

e) Sleep apnea

f) Hyper or hypothyroidism

g) Pheochromocytoma

h) Pre-eclampsia

i) Aortic coarctation

4) PHARMACOTHERAPY

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.

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

These include

a) Thiazide diuretics,

b) Calcium antagonists,

c) Angiotensin receptor blockers,

d) Beta blockers,

e) Alpha -1 receptor antagonists and

f) Angiotensin converting enzyme (ACE) inhibitor.

5) COMBINATION THERAPY

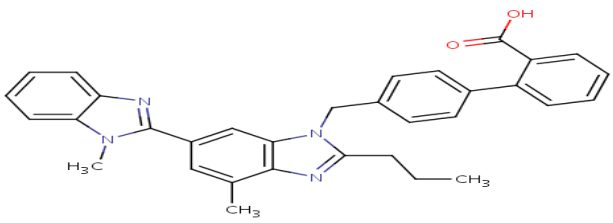
Most patients with concomitant hypertension and diabetes require more than one agent to attain adequate blood pressure control. In the HOT trial 68 percent of patients were maintained on combination antihypertensive therapy. The combination of ACE inhibitors and

CCBs (dihydropyridine or nondihydropyridine) is associated with a reduction in cardiovascular events and proteinuria. The combination of a dihydropyridine and a nondihydropyridine CCB has been shown to have a synergistic blood-pressure–lowering potential. Caution should be used with the combination of nondi- hydropyridine CCBs and beta blockers because of the potential for additive negative cardiac inotropic effects. Combinations of beta blockers and ACE inhibitors have shown few additive effects on blood pressure when used in patients with a pulse rate of less than 84 beats per minute. The final phase of the CALM study examined combination treatment with candesartan and lisinopril. Study participants showed good tolerance for the two agents together and a more effective reduction in blood pressure.

6) DRUG PROFILE

a) TELMISARTAN

Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension. Generally, angiotensin II receptor blockers (ARBs) such as telmisartan bind to the angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial blood pressure. Recent studies suggest that telmisartan may also have PPAR-gamma agonistic properties that could potentially confer beneficial metabolic effects. This compound belongs to the biphenyls and derivatives. These are organic compounds containing to benzene rings linked together by a C-C bondUsed alone or in combination with other classes of antihypertensives for the treatment of hypertension. Also used in the treatment of diabetic nephropathy in hypertensive patients with type 2 diabetes mellitus, as well as the treatment of congestive heart failure (only in patients who cannot tolerate ACE inhibitors).



Iupac names

2-(4-{[4-methyl-6-(1-methyl-1H-1,3-benzodiazol-2-yl)-2-propyl-1H-1,3-benzodiazol-1-yl]methyl}phenyl)benzoic acid.

Mechanism of action

Telmisartan interferes with the binding of angiotensin II to the angiotensin II AT_1-receptor by binding reversibly and selectively to the receptors in vascular smooth muscle and the adrenal gland. As angiotensin II is a vasoconstrictor, which also stimulates the synthesis and release of aldosterone, blockage of its effects results in decreases in systemic vascular resistance. Telmisartan does not inhibit the angiotensin converting enzyme, other hormone receptors, or ion channels. Studies also suggest that telmisartan is a partial agonist of PPARγ, which is an established target for antidiabetic drugs. This suggests that telmisartan can improve carbohydrate and lipid metabolism, as well as control insulin resistance without causing the side effects that are associated with full PPARγ activators.

Pharmacodynamics

Telmisartan is an orally active nonpeptide angiotensin II antagonist that acts on the AT_1 receptor subtype. It has the highest affinity for the AT_1receptor among commercially available ARBS and has minimal affinity for the AT_2 receptor. New studies suggest that telmisartan may also have PPARγ agonistic properties that could potentially confer beneficial metabolic effects, as PPARγ is a nuclear receptor that regulates specific gene transcription, and whose target genes are involved in the regulation of glucose and lipid metabolism, as well as anti-inflammatory responses. This observation is currently being explored in clinical trials. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Telmisartan works by blocking the vasoconstrictor and aldosterone secretory effects of angiotensin II.

Pharmacokinetics

Absolute bioavailability depends on dosage. Food slightly decreases the bioavailability (a decrease of about 6% is seen when the 40-mg dose is administered with food). Highly bound to plasma proteins (>99.5%), mainly albumin and a1-acid glycoprotein. Binding is not dose-dependent. Minimally metabolized by conjugation to form a pharmacologically inactive acylglucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan. Following either intravenous or oral administration of 14C-labeled telmisartan, most of the administered dose (>97%) was eliminated unchanged in feces

via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively). Bi-exponential decay kinetics with a terminal elimination half-life of approximately 24 hours.

Uses

This medication is used to treat high blood pressure (hypertension). Lowering high blood pressure helps prevent strokes, heart attacks and kidney problems. Telmisartan belongs to a class of drugs called angiotensin receptor blockers (ARBs). It works by relaxing blood vessels so blood can flow more easily. Used alone or in combination with other classes of antihypertensives for the treatment of hypertension. Also used in the treatment of diabetic nephropathy in hypertensive patients with type 2 diabetes mellitus, as well as the treatment of congestive heart failure (only in patients who cannot tolerate ACE inhibitors).

Side effects

Dizziness or lightheadedness may occur body adjusts to the medication. To reduce the risk of dizziness and lightheadedness, get up slowly when rising from a sitting or lying position. Remember that your doctor has prescribed this medication because he or she has judged that the benefit to you is greater than the risk of side effects. Many people using this medication do not have serious side effects.[7]

b) AMLODIPINE

Class

Dihydropyridines.

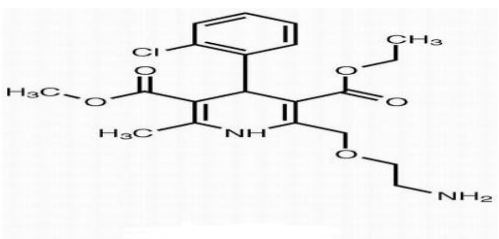
Chemical Name

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



Brands

Azor (combination), Caduet, Exforge (combination), Lotrel, Norvasc.

Mode of action

Amlodipine inhibits transmembrane influx of extracellular calcium ions across the membranes of myocardial cells and vascular smooth muscle cells, without changing serum calcium concentrations.[1] Amlodipine is a peripheral arterial vasodilator; acts directly on vascular smooth muscle causing reduction in peripheral vascular resistance and BP. Amlodipine reduces total peripheral resistance (afterload) and rate pressure product and thus myocardial oxygen demand at any given level of exercise in patients with exertional angina. Amlodipine blocks constriction and restores blood flow in coronary arteries in response to calcium, potassium, epinephrine, serotonin and thromboxane A_2 analog in animal studies and human vessels in vitro.

Pharmacokinetics

Absorption & Bioavailability

Peak plasma amlodipine concentrations attained 6–12 hours after oral administration. Absolute bioavailability ranges from 64–90%.

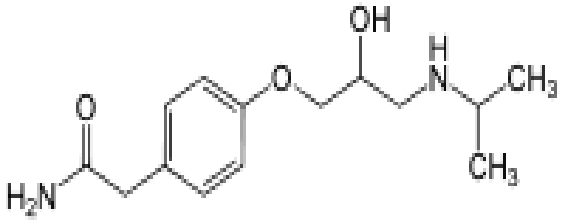
Duration

Antihypertensive effects of amlodipine persist for at least 24 hours after administration. The food does not affect bioavailability of amlodipine besylate tablets. The percentage of Plasma Protein Binding is 93%. It is extensively metabolized to inactive metabolites in the liver.

It is excreted in urine as metabolites (60%) and unchanged drug (10%). Terminal elimination half-life of amlodipine is 30–50 hours. In geriatric patients, amlodipine clearance decreased and AUC increased about 40–60%. In patients with hepatic impairment, amlodipine clearance decreased and AUC increased about 40–60%. In patients with moderate to severe heart failure, amlodipine clearance decreased and AUC increased about 40–60%.

c) ATENOLOL

It is β_1 receptor antagonist and the IUPAC name is (RS)-2-{4-[2-Hydroxy-3-(propan-2-ylamino)propoxy]phenyl}acetamide. The molecular formula is $C_{14}H_{22}N_2O_3$.



Mode of action

Inhibits response to adrenergic stimuli by competitively blocking β_1-adrenergic receptors within the myocardium. Blocks β_2-adrenergic receptors within bronchial and vascular smooth muscle only in high doses (e.g., >100 mg daily). Decreases resting and exercise-stimulated heart rate and reflex orthostatic tachycardia by about 25–35%.[c] Slows AV nodal conduction. No intrinsic sympathomimetic activity and little or no membrane-stabilizing effect on the heart. Reduces BP by decreasing cardiac output, suppressing renin release and/or decreasing sympathetic outflow from the CNS. In patients with angina pectoris, blocks catecholamine-induced increases in heart rate, myocardial contractility and BP, resulting in decreased myocardial oxygen consumption. Possibly increases oxygen requirements in patients with heart failure due to increased left ventricular fiber length and end diastolic pressure. Increases airway resistance (at doses >100 mg) in patients with asthma and/or COPD. Produces little or no changes in serum insulin concentrations, time to recovery from insulin-induced hypoglycemia, or free fatty acid response to hypoglycemia.

Dosage and Administration

Individualize dosage according to patient response. β_1-Adrenergic blocking selectivity diminishes as dosage is increased. If long-term therapy is discontinued, reduce dosage gradually over a period of about 2 weeks. It is Administer orally or by slow IV injection. Once-daily dosing usually is sufficient in the management of hypertension. After administration, we will moitor the heart rate, BP and ECG during IV therapy.

It may be administered undiluted by slow IV injection or diluted in dextrose injection, sodium chloride injection, or dextrose and sodium chloride injection prior to administration. For solution and drug compatibility information, see Compatibility under Stability. The rate of administer at a rate of 1 mg/minute.

Dosage

For Paediatric Patients with Hypertension (Oral)

Some experts recommend an initial dosage of 0.5–1 mg/kg daily given as a single dose or in 2 divided doses. Increase dosage as necessary up to a maximum dosage of 2 mg/kg (up to 100 mg) daily given as a single dose or in 2 divided doses.

For Adults with Hypertension (Oral)

Monotherapy: Initially, 25–50 mg once daily. Full hypotensive response may require 2 weeks. If necessary, increase to 100 mg once daily. Some patients may have improved BP control with twice-daily dosing.

Combination Therapy

Atenolol in fixed combination with chlorthalidone: initially, 50 mg of atenolol and 25 mg of chlorthalidone once daily. If response is not optimal, 100 mg of atenolol and 25 mg of chlorthalidone once daily.

Initial use of fixed-combination preparations is not recommended; adjust by administering each drug separately, then use the fixed combination if the optimum maintenance dosage corresponds to the ratio of drugs in the combination preparation. Administer separately for subsequent dosage adjustment.

May be added another antihypertensive agent when necessary (gradually using half of the usual initial dosage to avoid an excessive decrease in BP).

7) RESULTS AND DISCUSSION

a) 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 It 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 2: Baseline characteristics of patients

Parameters	Amlodipine/Telmisartan/ (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

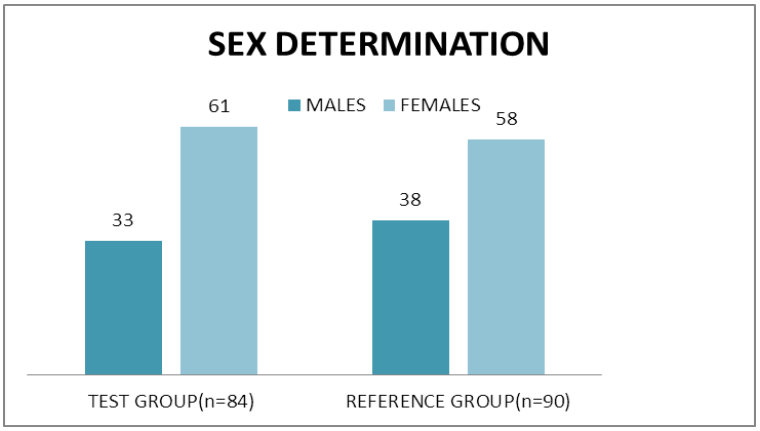


Figure 1:-Baseline Demographic Characteristic Variables Gender.

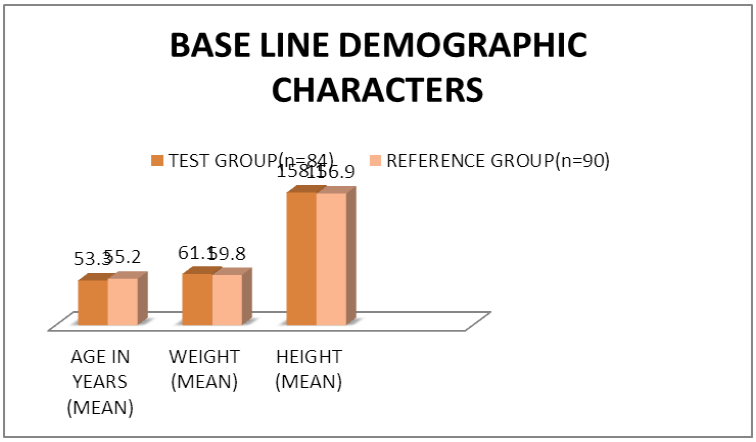


Figure 2:-Base Line Demographic Variables Age, Height and Weight.

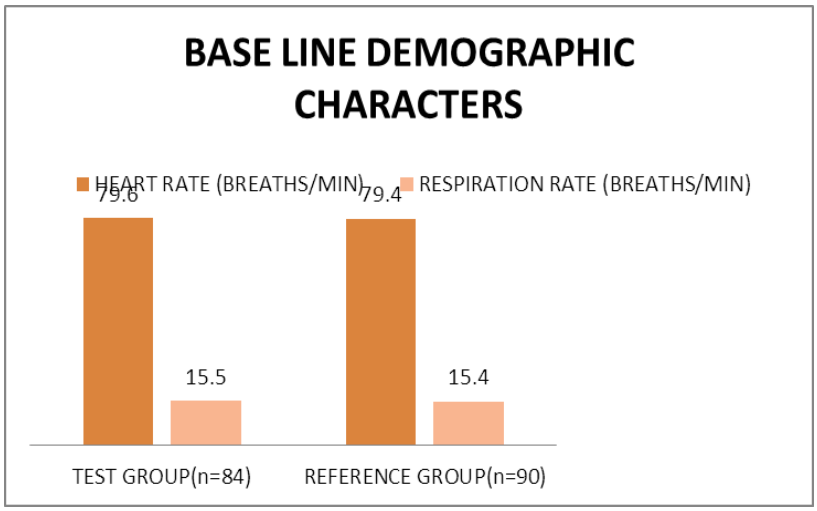


Figure 3:- Base Line Demographic Characteristic Variables Heart Rate, Respiratory Rate.

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 No. 3: 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

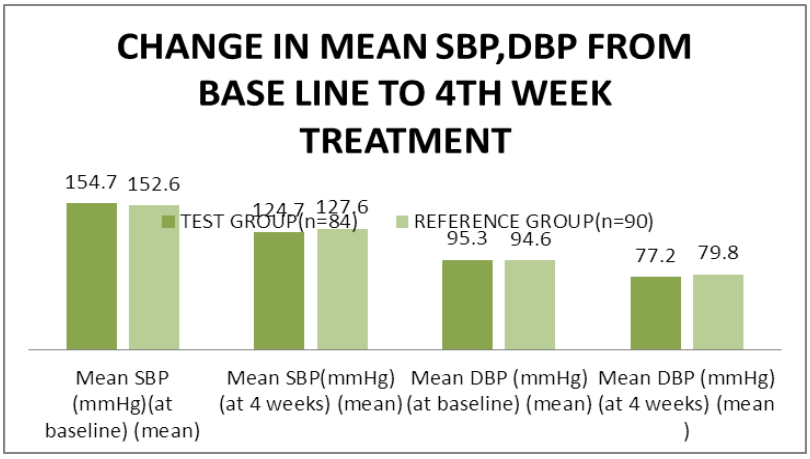


Figure 4:- Change In SBP and DBP At Baseline And After 4 Weeks.

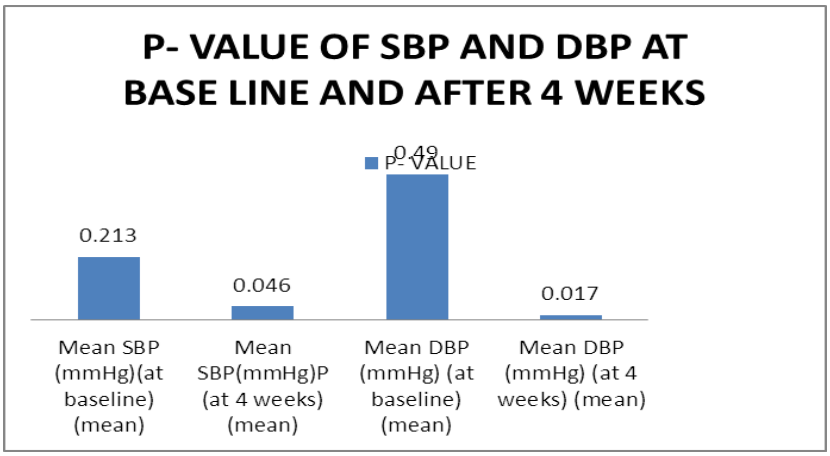


Figure 5:- P.Value of: Change In Sbp Snd Dbp at Baseline and After 4 Weeks.

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

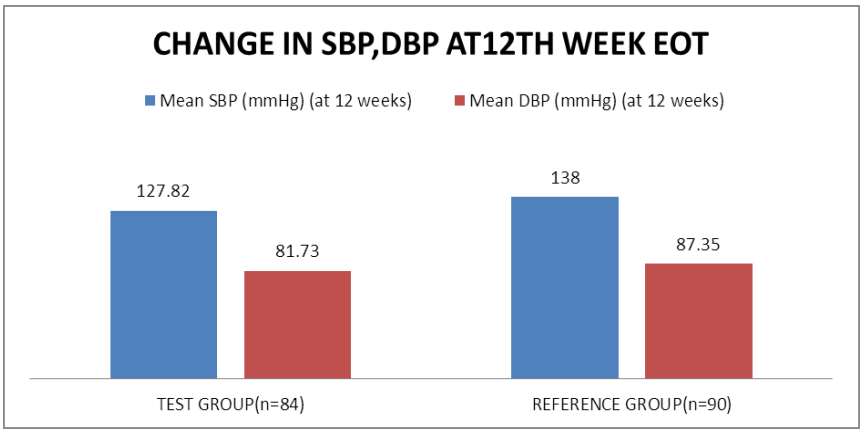


Figure 6:- Change In SBP and DBP after 12 Weeks of Treatment.

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	

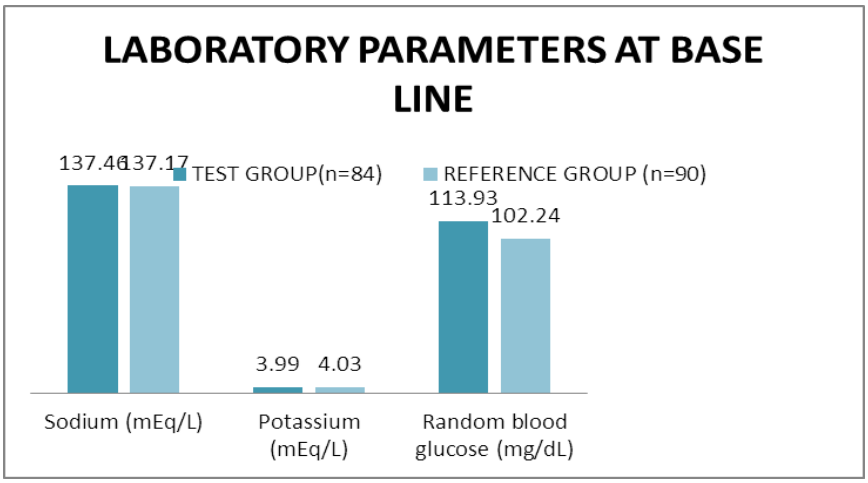


Figure 7: Laboratory Parameters.

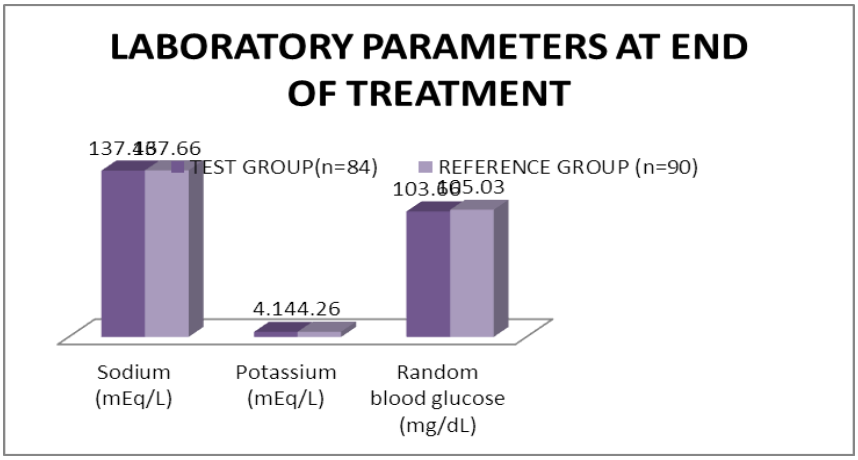


Figure 8: Laboratory Parameters.

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 aematology 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 and Nausea.

Side effects found with INVESTIGATIONAL PRODUCT

5.1.6.1 Headache -- in up to 9 percent of people.

5.1.6.2 Fatigue -- up to 5 percent.

5.1.6.3 Dizziness -- up to 4 percent.

5.1.6.4 Diarrhea -- up to 3 percent.

5.1.6.5 Nausea -- up to 3 percent.

5.1.6.6 Insomnia -- up to 1 percent.

b) 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 a angiotensin 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 besylate combination in comparison with atenolol/amlodipine alone. The result of this study showed that, telmisartan/amlodipine besylate 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 atenolol 25 mg, 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 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. Preliminary studies in stroke-prone spontaneously hypertensive rats have shown that significant synergism exists between atenolol and amlodipine in lowering and stabilizing blood pressure. The results of our study confirmed that the combination therapy with telmisartan/amlodipine besylate is superior to atenolol/Amlodipine combination therapy in patients with mild-to-moderate essential hypertension.

8) CONCLUSION

The study was conducted in PRIME 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/amlodipine besylate offers superior antihypertensive efficacy over atenolol/Amlodipine combination therapy in patients with mild-to-moderate essential hypertension.

9) SUMMARY

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. 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. 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.

The results of this study showed that, telmisartan/amlodipine besylate combination therapy with are superior to atenolol/amlodipine combination therapy with respect to mean fall in SBP, DBP, response rate and normalization of BP. The study was conducted in PRIME 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/amlodipine besylate offers superior antihypertensive efficacy over atenolol/Amlodipine combination therapy in patients with mild-to-moderate essential hypertension.

10) REFERENCES

1. Dunkler D, Kohl M, Teo KK, Heinze G, Dehghan M, Clase CM, Gao P, Yusuf S, Mann JF, Oberbauer R. Nephrol Dial Transplant. 2015 Aug; 30(4): iv76-iv85. doi: 10.1093/ndt/gfv086.
2. Bakheit AH, Abd-Elgalil AA, Mustafa B, Haque A, Wani TA. Profiles Drug Subst Excip Relat Methodol., 2015; 40: 371-429. doi: 10.1016/bs.podrm.2015.01.003. Epub 2015 Mar 31.
3. Lee E, Wu Z, Shon JC, Liu KH. Drug Metab Dispos., 2015 Aug; 43(8): 1250-3. doi: 10.1124/dmd.115.064345.
4. Estacio RO, Jeffers BW, Gifford N, Schrier RW. Diabetes Care. 2000 Apr; 23(2): B54-64. PMID: 10860192
5. Rosei CA, Withers SB, Belcaid L, De Ciuceis C, Rizzoni D, Heagerty AM. J Hypertens., 2015 May; 33(5): 1039-45. doi: 10.1097/HJH.0000000000000506.
6. Motozato K, Miura SI, Shiga Y, Kusumoto T, Adachi S, Inoue T, Fujisawa K, Saku K. Clin Exp Hypertens., 2015 Aug; 13: 1-6. [Epub ahead of print].
7. Bramlage P, Fronk EM, Wolf WP, Smolnik R, Sutton G, Schmieder RE. Vasc Health Risk Manag., 2014 Dec 17; 11: 1-8. doi: 10.2147/VHRM.S75380. eCollection 2015.
8. Lawrence Gould A, Unniachan S, Wu D. Int J Clin Pract., 2014 Feb; 68(2): 163-72. doi: 10.1111/ijcp.12343. Review.
9. vanovic B, Tadic M. J Cardiovasc Pharmacol Ther., 2013 Nov; 18(6): 544-9. doi: 0.1177/1074248413492907. Epub 2013 Jul 5.
10. Morris KF, Billiot EJ, Billiot FH, Hoffman CB, Gladis AA, Lipkowitz KB, Southerland WM, Fang Y. Chem Phys., 2015 Aug 18; 457: 133-146.
11. Ahrens K, Bramlage P. Drugs Today (Barc)., 2010 May; 46(5): 339-50. doi: 10.1358/dot.2010.46.5.1469896. Review.

12. Arif AF, Kadam GG, Joshi C. J Indian Med Assoc., 2009 Oct; 107(10): 730-3.
13. Assaad-Khalil SH, Najem R, Sison J, Kitchlew AR, Cho B, Ueng KC, DiTommaso S, Shete A. Vasc Health Risk Manag., 2015 Jan 21; 11: 71-8. doi: 10.2147/VHRM.S76599. eCollection 2015.
14. Sison J, Assaad-Khalil SH, Najem R, Kitchlew AR, Cho B, Ueng KC, Shete A, Knap D. Curr Med Res Opin., 2014 Oct; 30(10): 1937-45. doi: 0.1185/03007995.2014.942415.
15. Lawrence Gould A, Unniachan S, Wu D. Int J Clin Pract., 2014 Feb; 68(2): 163-72. doi: 10.1111/ijcp.12343. Review.
16. Mahu ŞC, Hăncianu M, Agoroaei L, Grigoriu IC, Strugaru AM, Butnaru E. Rev Med Chir Soc Med Nat Iasi., 2015 Apr-Jun; 119(2): 585-91.
17. Bakheit AH, Abd-Elgalil AA, Mustafa B, Haque A, Wani TA. Profiles Drug Subst Excip Relat Methodol., 2015; 40: 371-429. doi: 10.1016/bs.podrm.2015.01.003.
18. Machalke K, Bramlage P, Bramlage K, Tebbe U. Dtsch Med Wochenschr., 2015 Apr; 140(8): 590-2. doi: 10.1055/s-0041-101294. Epub 2015 Apr 16. German.
19. Prathab Balaji S, Vijay Chand C, Justin A, Ramanathan M. Pharmacol Biochem Behav. 2015 Aug 8. pii: S0091-3057(15)30044-7. doi: 10.1016/j.pbb.2015.08.007.
20. Dogotar O, Sopetik V, Kotovskaya Y. J Hypertens., 2015 Jun; 33(1): e103. doi: 10.1097/01.hjh.0000467629.01505.b1.
21. Lacy PS, Brunel P, Bader G, Jones A, Baschiera F, Düsing R, Williams B. J Renin Angiotensin Aldosterone Syst. 2015 May 5. pii: 1470320315579592.
22. *Wang TJ, Ausiello JC, Stafford RS.* "Trends in Antihypertensive Drug Advertising". *Circulation, 1999; 99: 2055–7.*
23. T Ishizaki, Y Oyama, T Suganuma, T Sasaki, H Nakaya, A dose ranging study of atenolol in hypertension: fall in blood pressure and plasma renin activity, beta-blockade and steady-state pharmacokinetics.