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Pharmacology

COMPARISON OF EFFICACY OF TELMISARTAN AND AMLODIPINE IN PATIENTS OF HYPERTENSION PRESCRIBED AS FREE DRUG AND AS FIXED DOSE COMBINATION.

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ABSTRACT **INTRODUCTION:** HTN remains one of the major preventable risk factors for coronary events, cerebral-vascular disease, heart failure, peripheral vascular disease and progression of kidney disease. Most patients with HTN will require more than one drug to achieve BP target. In addition, around 24% to 32% of patients will require a combination of more than two drugs to achieve BP targets. Combination therapy for HTN may be delivered either as free or fixed drug combinations. In a free drug combination, each BP-lowering drug is administered in a separate pill, while in a fixed drug combination two or more agents are combined in a single pill (SPC). SPCs may offer several advantages over free drug combinations, such as better compliance and simplicity of treatment.

MATERIAL AND METHOD: Study was conducted for a span of one year. Every patient coming to medicine OPD for the treatment of hypertension, who has already been prescribed 40mg Telmisartan or 5mg amlodipine individually were included also the newly diagnosed patients for essential hypertension were included. **INCLUSION CRITERIA:** (a) 18- 60 years, Adults of either sex (b) Newly diagnosed patients of essential hypertension (c) Already diagnosed old patients on treatment for essential hypertension with 40mg Telmisartan or 5mg Amlodipine. **EXCLUSION CRITERIA:** (a) Patients with chronic diseases e.g. Diabetes mellitus, CKD & CAD(b) Pregnant & lactating females.

RESULTS: Total 267 patients were enrolled in the study. Age and sex wise distribution was given in table no. 1.1. 138 patients were started on telmisartan and amlodipine free drug and 129 patients were started on telmisartan and amlodipine fixed drug. Majority of patients were less than 60 years and 121(45.3%) patients were male and 146(54.7%) patients were female. 138 Patients were started on telmisartan and amlodipine free drug group. 28.3% patients were on amlodipine and 25.4% patients were on telmisartan where as 46.4% patients were not taking any antihypertensive treatment and mean systolic and diastolic blood pressure in this group was 168.3±**14.2:** 95.4±**7.2**. 129 patients were started on telmisartan and amlodipine fixed dose combination. 31% patients were on amlodipine and 24.8% patients were on telmisartan where as 44.2% were not taking any drugs and mean systolic and diastolic blood pressure in this group was 167.8±**15.6:** 95.7±**7.1**.

CONCLUSION: Telmisartan/amlodipine combination when administered separately at different times of the day showed good to excellent responsea

KEYWORDS :

INTRODUCTION

Arterial Hypertension (HTN) is a highly prevalent chronic disease, with estimates reaching 26% of the worldwide adult population[1]. In the United States, the prevalence of HTN reached 30%, as defined by a systolic blood pressure (BP) of 140 mmHg or higher, a diastolic BP of 90 mmHg or higher, or currently using BP-lowering drugs[2]. HTN remains one of the major preventable risk factors for coronary events, cerebral-vascular disease, heart failure, peripheral vascular disease and progression of kidney disease[3-5]. Hypertension accounts for 35% of cerebrovascular diseases and 21% of ischemic heart diseases, suggesting the importance of hypertension management because it means that 35% of cerebrovascular diseases and 21% of ischemic heart diseases are preventable if normal blood pressure (BP) could be maintained in the population. Most patients with HTN will require more than one drug to achieve BP target, and mono-therapy would only be sufficient in about 20–30% of patients[6]. In addition, around 24% to 32% of patients will require a combination of more than two drugs to achieve BP targets[7-8]

In a recent meta-analysis, a target systolic BP of less than 130 mmHg significantly decreased the incidence of cardiovascular events, and in the recently published SPRINT trial, a mean number of BP medications of 2.8 was required to achieve a mean systolic BP of 121.5 mmHg in the intensive treatment group, which resulted in a 25% lower relative risk of cardiovascular events as compared to the standard-treatment group[9,10].

Proper BP control at an early stage is essential for high-risk patients with hypertension. Hypertension is not easily controlled with only a single agent unless it is mild, and dual combination therapy is recommended from the first for patients with stage 2 or higher hypertension or for high-risk patients [11]

Combination therapy for HTN may be delivered either as free or fixed drug combinations. In a free drug combination, each BP-lowering drug is administered in a separate pill, while in a fixed drug combination two or more agents are combined in a single pill (SPC). SPCs may offer several advantages over free drug combinations, such as better compliance and simplicity of treatment[12]. The recently updated European guidelines have advocated SPCs as the preferred approach to combine BP-lowering drugs[13].

The objective of this study is to compare BP lowering effects of a fixed versus free combination of two BP-lowering agents on in patients with essential HTN.

MATERIALS AND METHODS:

Study was conducted for a span of one year. Every patient coming to medicine OPD for the treatment of hypertension, who has already been prescribed 40mg Telmisartan or 5mg amlodipine individually were included also the newly diagnosed patients for essential hypertension were included.

INCLUSION CRITERIA:

(a) 18- 60 years, Adults of either sex
(b) Newly diagnosed patients of essential hypertension
(c) Already diagnosed old patients on treatment for essential hypertension with 40mg Telmisartan or 5mg Amlodipine.

EXCLUSION CRITERIA:

(a) Patients with chronic diseases e.g. Diabetes mellitus, CKD & CAD
(b) Pregnant & lactating females

Detailed methodology

Study Setting:
Study was conducted in hypertensive patients coming to DR RKGMC, Hamirpur (HP) for one year

Study Population:

Patients coming to medicine OPD for the treatment of essential

hypertension over a period of one year were included after screening and they were divided into two groups.

Study design: An observational comparative study

DATA COLLECTION:
Patients: The patients fulfilling the inclusion criteria and who are willing to give written informed consent will be included in the study. Information about socio demographic profile, history of illness, personal history, and treatment history will be collected using a pretested schedule .

Study was conducted for a span of one year. Every patient coming to medicine OPD for the treatment of essential hypertension, who was taking 40mg Telmisartan in the morning after breakfast and 5mg amlodipine after dinner separately, were included in the study and efficacy of 40mg Telmisartan and 5mg amlodipine separately will be compared with fixed dose combination of 40mg Telmisartan and 5mg amlodipine. Pregnant and lactating women and patients with hypertensive emergencies and consuming drugs for other diseases were excluded. Systolic & diastolic blood pressure of the patient was recorded and patients with more than 120mm of Hg (systolic BP). & more than 80mm of Hg (diastolic BP) were enrolled in the study, after obtaining informed consent from the patients (Annexure-II). Patients will be reviewed every 4th week for duration of 3 months (total 3 reviews). An objective of the study is to lower systolic BP by 20 mm of Hg & diastolic BP by 10 mm of Hg.

RESULTS:
Total 267 patients were enrolled in the study. Age and sex wise distribution was given in table no. 1.1. 138 patients were started on telmisartan and amlodipine free drug and 129 patients were started on telmisartan and amlodipine fixed drug. Majority of patients were less than 60 years and 121(45.3%) patients were male and 146(54.7%) patients were female.

TABLE 1.1 Age and sex distribution:

	TELMISARTAN + AMLODIPINE free drug (N = 138)	TELMISARTAN + AMLODIPINE Fixed dose combination (N = 129)	Total (N = 267)
Age group wise distribution (p value = 0.48)			
20 – 40 years	54(39.1%)	45(34.9%)	99(37.1%)
41 – 60 years	70(50.7%)	63(48.8%)	133(49.8%)
61 -80 years	12(8.7%)	19(14.7%)	31(11.6%)
≥ 81years	02(1.4%)	02(1.6%)	04(1.5%)
Mean ± S. D	46.3±12.8	47.2±13.2	46.6±12.9
Sex distribution (p value = 0.38)			
Male	59(42.8%)	62(48.1%)	121(45.3%)
Female	79(57.2%)	67(51.9%)	146(54.7%)

138 Patients were started on telmisartan and amlodipine free drug group. 28.3% patients were on amlodipine and 25.4% patients were on telmisartan where as 46.4% patients were not taking any antihypertensive treatment and mean systolic and diastolic blood pressure in this group was 168.3±**14.2:** 95.4±**7.2**. 129 patients were started on telmisartan and amlodipine fixed dose combination. 31% patients were on amlodipine and 24.8% patients were on telmisartan where as 44.2% were not taking any drugs and mean systolic and diastolic blood pressure in this group was 167.8±**15.6:** 95.7±**7.1**. (table 1.2)

Table 1.2. Baseline blood pressure and anti-hypertensive treatment:

	TELMISARTAN + AMLODIPINE free drug (N = 138)	TELMISARTAN + AMLODIPINE Fixed dose combination (N = 129)	Total (N = 267)
Initial anti-hypertensive treatment			
Amlodipine	39(28.3%)	40(31.0%)	79(29.6%)
Telmisartan	35(25.4%)	32(24.8%)	67(25.1%)
No drug	64(46.4%)	57(44.2%)	121(45.3%)
Baseline blood pressure (SBP p value = 0.77; DBP p value = 0.66)			
Systolic B. P	168.3±**14.2**	167.8±**15.6**	167.6±**14.8)**
Diastolic B. P	95.4±**7.2**	95.7±**7.1**	95.5±**7.1)**

After 4 weeks of taking drugs in both groups there is significant blood pressure reduction in telmisartan and amlodipine free drug group and 55.1 % patients has controlled blood pressure compared to telmisartan and amlodipine fixed drug patients where only 29.5%have controlled blood pressure with p value <0.0001 (table 1.3)

Table 1.3. Blood pressure status at 4 weeks:

	TELMISARTAN + AMLODIPINE free drug (N = 138)	TELMISARTAN + AMLODIPINE Fixed dose combination (N = 129)	Total (N = 267)
Blood pressure controlled	76(55.1%)	38(29.5%)	114(42.6%)
Not controlled	62(44.9%)	91(70.5%)	153(57.3%)
Total	**138**	**129**	**267**
Odd ratio 3.09 ;95%CI:(1.85 – 5.16); p value< 0.0001			

After 8 weeks of taking drugs in both groups there is significant blood pressure reduction in telmisartan and amlodipine free drug group. 75.1 % patients have controlled blood pressure compared to telmisartan and amlodipine fixed drug patients where only 34.1%have controlled blood pressure with p value <0.0001 (table 1.4)

Table 1.4 Blood pressure control at 8 weeks:

	TELMISARTAN + AMLODIPINE free drug (N = 138)	TELMISARTAN + AMLODIPINE Fixed dose combination (N=129)	Total (N = 267)
Blood pressure controlled	104(75.4%)	44(34.1%)	148(55.4%)
Not controlled	34(26.6%)	85(65.9%)	119(44.6%)
Total	138	129	267
Odd ratio 5.9 ;95%CI:(3.47 – 10.05); p value< 0.0001			

Table: Blood pressure control in free drug group

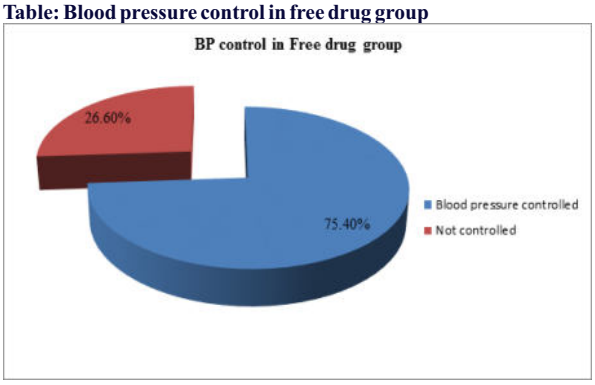
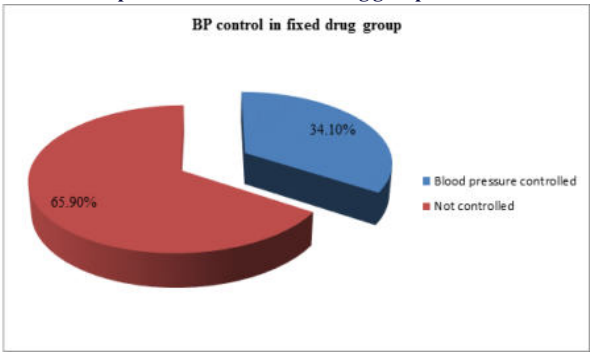


Table: Blood pressure control in free drug group



Blood pressure reduction at 4 and 8 weeks is shown in Table no.1.5 and 1.6 in both the group which shows that there is significant systolic and diastolic blood pressure reduction in free drug group.

Table 1.5 Status of systolic and diastolic blood pressure in free drug group:

	Baseline B.P	At 4 weeks	At 8weeks	P value
Systolic B.P	168.3±14.2	135.3±12.0	130.8±12.2	**<0.01**
Diastolic B.P	95.4±7.1	81.8±6.3	80.8±6.2	**<0.01**

Table: Status of systolic and diastolic blood pressure in free drug group

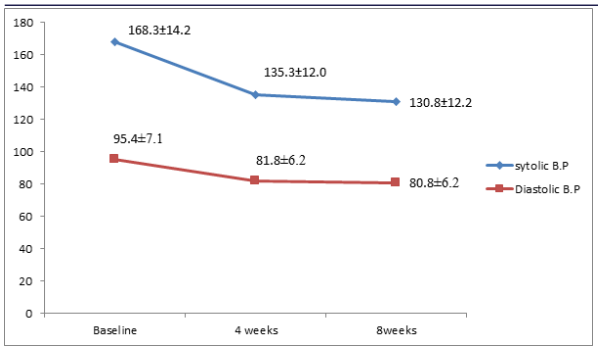
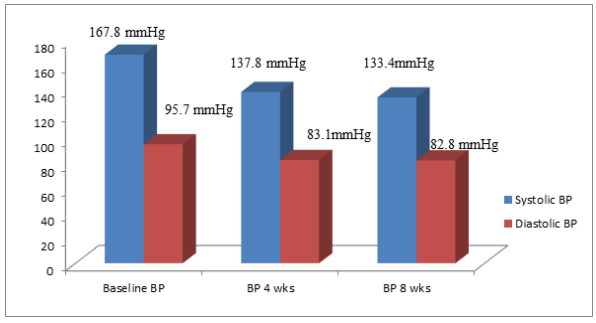


Table 1.6. Status of systolic and diastolic blood pressure in fixed drug group:

	Baseline B.P	At 4 weeks	At 8weeks	P value
Systolic B.P	167.8±15.6	137.8±11.9	133.4±11.2	**<0.01**
Diastolic B.P	95.7±7.0	83.1±6.2	82.8±5.4	**<0.01**



DISCUSSION

Telmisartan and Amlodipine are two efficacious antihypertensives with fewer side effects that would be able to achieve the desired goal of maintaining greater reduction in B.P.

Telmisartan, in addition to blocking the angiotensin II type 1 receptor, activates the peroxisome proliferator-activated receptor (PPAR)-gamma a well-known target for treatment of the metabolic syndrome and diabetes. By contrast, other angiotensin-receptor blockers do not have activity on PPAR-gamma. Telmisartan is a partial agonist of PPAR-gamma and has a superior tolerability profile without causing the fluid retention and edema associated with full agonists of PPAR-gamma.

In addition to antidiabetic properties, PPAR-gamma activators may also provide protection against atherosclerosis and coronary events. Calcium antagonists are recommended as a therapeutic medicine for diabetic hypertensive patients, because they have no adverse influence on lipid metabolism or glucose metabolism. The combination thus helps in treatment of hypertension especially beneficial with those who have concomitant diabetes or metabolic syndrome and thus prevents atherosclerotic cardiovascular disease.

In the present study the status of baseline mean SBP was 168.3±14.2mm Hg which dropped to 135.3 ± 12.0 mm Hg at 4 weeks and further dropped to 130.8 ± 12.2mm Hg at 8 weeks in free drug group when administered separately and it was found statistically very significant ($p<0.0001$). The status of baseline mean SBP in case of fixed drug group was 167.3±15.6mm Hg which dropped to 137.8 ± 11.9mm Hg at 4 weeks and further dropped to 133.4 ± 11.2 mm Hg at 8 weeks and it was found statistically very significant ($p<0.0001$). Also the baseline mean DBP was 95.7± 7.0mm Hg which dropped to 82.8 ± 5.4 mm Hg at 8 weeks in case of fixed drug (statistically significant) and with free drug mean DBP at 8 weeks was 80.8± 6.2 mm Hg as compared to 95.4± 7.1mm Hg at baseline which was found to be statistically significant.

Patients with hypertension are a heterogeneous population encompassing many hypertensive phenotypes. Hence, combination therapy with pharmacologic action on two or more different physiological sites is expected to be more effective, as it blocks the counter regulatory responses generally associated with mono-therapy and its mostly single site of action.

Available clinical trial data suggest that the telmisartan /amlodipine combination pill is a safe efficacious option for the long-term treatment of hypertension. The complementary mechanisms of its components appear to enhance the effectiveness beyond that provided by each drug alone, including potential synergistic effects on endothelial function, while reducing some of the negative effects produced by amlodipine, such as peripheral edema. Furthermore, the potential effect(s) of telmisartan on the cardio protective ACE2-ang (1-7)-Mas receptor axis may provide added benefits that have yet to be fully elucidated. Additional long-term data in hypertensive women and minorities may be warranted to further confirm the safety and efficacy of the telmisartan/amlodipine combination pill in these populations.

CONCLUSION

Combined antihypertensive therapy plays a crucial role in achieving targeted blood pressure reductions. Telmisartan/amlodipine combination when administered separately at different times of the day showed good to excellent response in 55.1% of the cases at 4 weeks as compared to 29.5% of the cases in FDC group and 75.4 % patient's achieving JNC VIII recommended goals over 8 weeks period in separate pill group as compared to 34.1% in FDC group.

REFERENCES

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet (London, England). 2005; 365(9455):217–23.
2. Vital signs: prevalence, treatment, and control of hypertension—United States, 1999–2002 and 2005–2008. MMWR Morb Mortal Wkly Rep. 2011; 60 (4):103–8.
3. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation. 2012.
4. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. Jama. 1996; 275(20):1557–62. Epub 1996/05/22. PMID: 8622246.
5. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. The New England journal of medicine. 1992; 326 (6):381–6.
6. Morgan TO, Anderson AI, MacInnis RJ. ACE inhibitors, beta-blockers, calcium blockers, and diuretics for the control of systolic hypertension. American journal of hypertension. 2001; 14(3):241–7.
7. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet (London, England). 1998; 351(9118):1755–62.
8. Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. The New England journal of medicine. 2008; 359 (23):2417–28.
9. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet (London, England). 2015.
10. Wright JT Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. The New England journal of medicine. 2015; 373(22):2103–16.
11. 2007ESH-ESCGuidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hyper- tension (ESH) and of the European Society of Cardiology (ESC). Blood Press. 2007; 16:135–232.
12. Zhu D, Gao P, Yagi N, Schumacher H.Efficacy and tolertability of Telmisartan Plus Amlodipine in Asian Patients Not Adeququatly Controllede on Either Monotherapy or on Low-Dose Combination Therapy. International Journal of Hyperttension. 2014;1–11.
13. Lacourciere Y, Lenis J, Orchard R. A comparision of efficacies and duration of action of the angiotensin II receptor blocker telmisartan and amlodipine. Blood pressure Monitoring.1998;295–302.