Section: Pharmacology

Original Research Article

THE ANTI-HYPERTENSIVE EFFECTS OF HIGH DOSE TELMISARTAN AND LOW DOSE COMBINATION THERAPY TELMISARTAN + AMLODIPINE IN PATIENTS WITH HYPERTENSION, AT GGH, BY DEPARTMENT OF PHARMACOLOGY, KURNOOL MEDICAL COLLEGE, KURNOOL, ANDHRA PRADESH - A PROSPECTIVE STUDY"

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ABSTRACT

Hypertension is defined as a systolic blood pressure (SBP) of 140 mm Hg or more, or a diastolic blood pressure (DBP) of 90 mm Hg or more. Globally, an estimated 26% of the world's population (972 million people) has hypertension, and the prevalence is expected to increase to 29% by 2025, driven largely by increase in economically developing nations. Hypertension affects one in four individuals worldwide. ARBs, CCBs are first line of therapy of hypertension and has out shifted the use of ACEIs. Telmisartan is the preferable ARB, Amlodipine a third generation CCB are commonly prescribed for hypertension in INDIA. Telmisartan has a very high lipophilicity and high volume of distribution which offers advantage of good tissue penetration over other sartans. Amlodipine a DHPs of CCBs is prescribed because of less negative inotropic and high vascular selectivity.

The present study comprises of 60 patients (both men and women) of 18 and above age, who are suffering from idiopathic hypertension to know the efficacy of low dose combination therapy of Telmisartan(40mg) with Amlodipine (5mg) against high dose monotherapy of Telmisartan(80mg).

In present study, a low dose combination therapy of Telmisartan 40mg + Amlodipine 5mg has demonstrated significantly greater BP reduction in both SBP and DBP compared to high dose monotherapy with Telmisartan 80mg.The combination therapy with Telmisartan 40mg + Amlodipine 5mg is well tolerated with a safety profile similar to the monotherapy with Telmisartan 80mg.

Keywords: CCB- Calcium channel blocker, ARB- Angiotensin receptor blocker, SBP-Systolic blood pressure, DBP- Diastolic blood pressure.

INTRODUCTION

The 2017 ACC/AHA guidelines eliminate the classification of prehypertension and divides it into two levels.[1,2] Elevated blood pressure with a systolic pressure between 120 and129 mm Hg and diastolic pressure less than 80 mm Hg. Stage 1 hypertension, with a systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 80 to 89 mm Hg. Most cases of hypertension are idiopathic, which is also known as essential hypertension. It has long been suggested that an increase in salt intake and lack of physical activity increases the risk of developing hypertension.[3] One of the described

factors for the development of essential hypertension is the patient's genetic ability to salt response.[4,5] About 50% to 60% of the patients are salt sensitive and therefore tend to develop hypertension.[6] This study takes patients with essential hypertension into perspective. Low dietary intake of calcium and potassium also may contribute to the risk of hypertension.[7]

Secondary causes include heart and kidney diseases, this form of hypertension may become less refined independent.[7] The ratio of circulating prorenin to renin is markedly elevated in diabetes, which may be causative in nephropathy and retinopathy.[8]

Hypertension is a well-recognized risk factor for cardiovascular and renal diseases; moreover, even slightly elevated blood pressure (BP) levels lead to increased risk in cardiovascular diseases (CVD) or stroke.[9]

The present study is aimed at comparing the response of hypertensive patients to therapy with high dose Telmisartan monotherapy and low dose combination therapy with Telmisartan-Amlodipine. This study includes examining the response of 60 patients to 2 kinds of drug regimen; 30 patients receiving high dose Telmisartan monotherapy and another 30 patients receiving low dose combination therapy with Telmisartan-Amlodipine. The outcome of the data compiled suggests which drug regimen is more effective in achieving the desired reduction in blood pressure in patients diagnosed with essential hypertension.

MATERIAL AND METHODS

The study is conducted in outpatient and inpatient department of General Medicine, government general hospital, Kurnool, Andhra Pradesh. Patients are divided into two groups based on type of medication received for essential hypertension as prescribed by the clinician. The study has been conducted after receiving approval from institutional Ethics Committee and only patients who met the study criteria and have given written informed consent are enrolled as study participants.

Participation in the study was voluntary and they had right to withdraw from the study at any point of time, and new patients are replaced. Group A with 30 patients receiving 80 mg Telmisartan monotherapy and group B with 30 patients receiving combination therapy of Telmisartan- Amlodipine [40 mg +5 mg] for a period of 8 weeks. If a dose is missed by the patient, they are instructed to take the next dose as per schedule. The response of the patient to the medication in the form of fall in systolic [SBP] and diastolic blood pressure [DBP] is noted in the two groups using a sphygmomanometer to the nearest 2mm of Hg and the data is compared for interpretation. All the adverse drug reactions occurring due to the antihypertensives prescribed during the course of the trial are also recorded.

Inclusion Criteria

1. Patients aged 18years or more who are diagnosed with hypertension and prescribed antihypertensives.
2. Patients who have given consent.

Exclusion Criteria

1. Patients diagnosed with other cardiac or renal disorders.
2. Patients on medications that can interact with Telmisartan or Amlodipine.
3. Pregnancy and nursing mothers.
4. Patients who have poor compliance with the drugs.
5. Patients with hypersensitivity to any of the medications used for the study.

Statistical Analysis

The data obtained from the study will be summarized to mean, standard deviation and all continuous variables and discreet variables will be compared using paired t test and P value <0.05 is considered significant.

RESULTS

The study was conducted in GOVERNMENT GENERAL HOSPITAL, KURNOOL from August 2023 for a period of two months in the outpatients and inpatients of Department of General Medicine. The study sample consists of 60 patients who were diagnosed with essential hypertension into two groups of one with high dose(80mg) Telmisartan monotherapy (30 patients) and the other with low dose combination therapy of Telmisartan(40mg)-Amlodipine(5mg) (30 patients).

The results are discussed under the following section

A) The highest number of participants in the study were over the age of 60 years (50% total subjects -30), most of the participants in this group (33.7% total subjects (11)) were prescribed low dose combination of Telmisartan 40mg + Amlodipine 5mg and the remaining subjects (19-66.3%) were prescribed high dose monotherapy with Telmisartan 80mg. The next major proportion of the subjects were from the 50-60 years age group (31.6% subjects-19), and prescribed Telmisartan 80mg (57.8%-11) and Telmisartan 40mg + Amlodipine 5mg (42.1%-8). This was followed by the 40-50 years age group (18.3%-11), in this group were mostly prescribed Telmisartan 80mg (72.7%-8), followed by Telmisartan 40mg + Amlodipine 5mg (27.2%-3).

B) In this study, the proportion of male participants (56.6%) was slightly greater than that of the female participants (43.3%) and indicates that the age-standardized incidence of hypertension is slightly higher in males than in females.

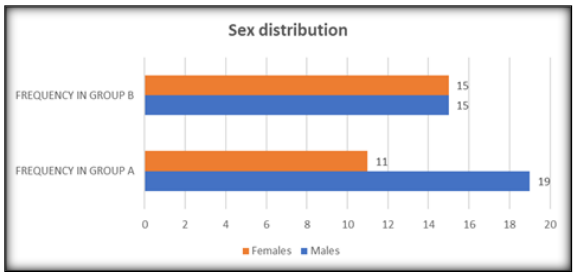

Figure 1: shows the frequency of sex distribution of hypertensive patients who participated in the study, the frequency is slightly more in males compared to females

C) Effect of treatment on SBP of the participants: In this study, the fall in mean SBP observed in group B (treated by Telmisartan 40mg + Amlodipine 5mg) was greater than that observed in group A (treated by Telmisartan 80mg). The reduction in SBP observed were 22 vs 16 mm of Hg in group B and group A respectively.

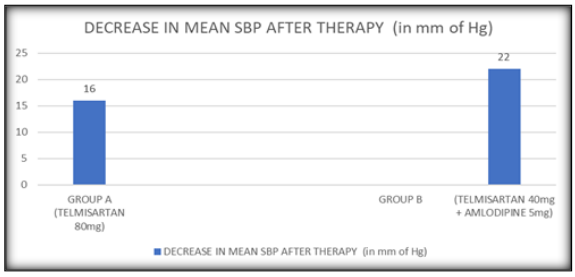

Figure 2: Shows the effect of treatment on mean SBP of the participants, the fall in SBP is 16mm of Hg in Group A consisting of patients receiving Telmisartan 80mg and 22mm of Hg in Group B consisting of patients receiving combination of Telmisartan 40mg + Amlodipine 5mg

D) Effect of treatment on DBP of the participants
In this study, the fall in mean DBP observed in group B (treated by Telmisartan 40mg + Amlodipine 5mg) was greater than that observed in group A (treated by Telmisartan 80mg). The reduction in DBP observed were 16 vs 10 mm of Hg in group B and group A respectively.

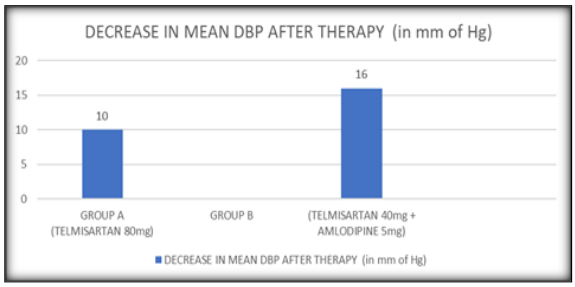

Figure 3: Shows the effect of treatment on mean DBP of the participants, the fall in DBP is 10mm of Hg in Group A consisting of patients receiving Telmisartan 80mg and 16mm of Hg in Group B consisting of patients receiving combination of Telmisartan 40mg + Amlodipine 5mg.

E) Percentage of patients who achieved SBP control (<140 mm of Hg)

In this study, 63.3% patients in Group A receiving Telmisartan 80mg had achieved SBP control by the 8th week while 83.3% in Group B receiving Telmisartan 40mg + Amlodipine 5mg had achieved SBP control by 8th week respectively.

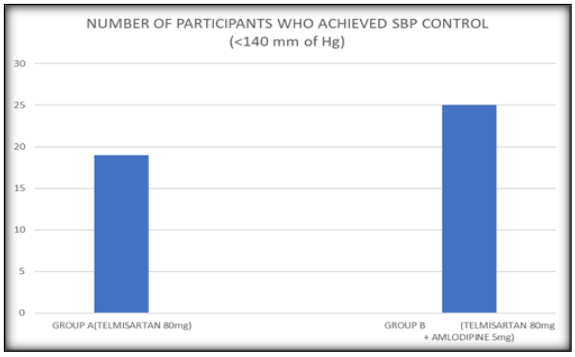

Figure 4: shows that 19 of the 30 participants (63.3%) in Group A receiving Telmisartan 80mg had achieved SBP control by the 8th week while 25 of the 30 participants (83.3%) in Group B receiving Telmisartan 40mg + Amlodipine 5mg had achieved SBP (<140mm of Hg) control by 8th week

F) Percentage of patients who achieved DBP control (<90 mm of Hg)

In this study, 86.6% participants in Group A receiving Telmisartan 80mg had achieved DBP control by the 8th week while 90% participants in Group B receiving Telmisartan 40mg + Amlodipine 5mg had achieved DBP control by 8th week.

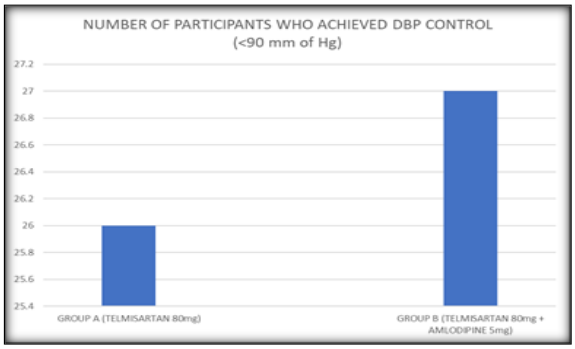

Figure 5: Shows that 26 of the 30 participants (86.6%) in Group A receiving Telmisartan 80mg had achieved DBP control by the 8th week while 27 of the 30 participants (90%) in Group B receiving Telmisartan 40mg + Amlodipine 5mg had achieved DBP control (<90mm of Hg) by 8th week.

G). 7 Incidence of Adverse drug reactions (ADRs) occurring in the participants during the course of the study: In this study, the incidence of ADRs observed in group A (13.3%) receiving Telmisartan 80mg was found to be higher than that observed in group B (10%) receiving Telmisartan 40mg + Amlodipine 5mg.

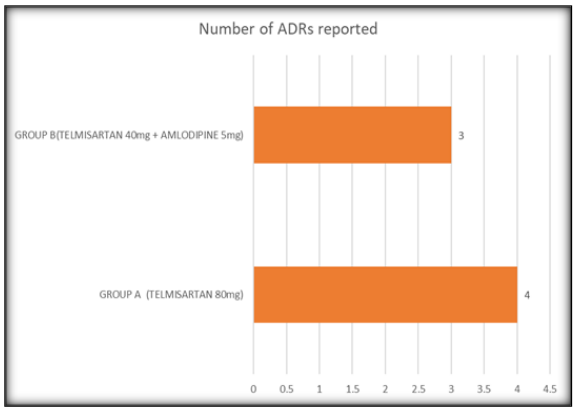

Figure 6: shows the frequency of ADRs reported in the treatment groups, it shows that 4 ADRs (13.33%) were reported in the Group A comprising of patients receiving Telmisartan 80mg and only 3 ADR (10%) was reported in the Group B comprising of patients receiving Telmisartan 40mg + Amlodipine 5mg.

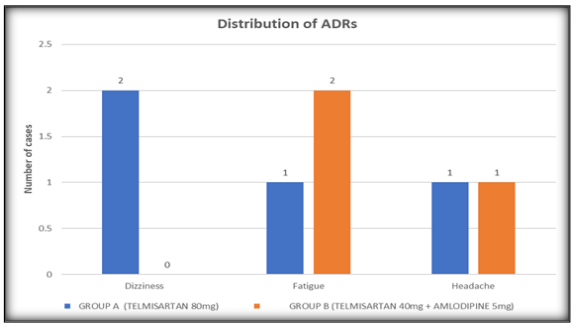

Figure 7: Shows the distribution of ADRs reported in the study and it shows that out of the 7 ADRs reported in the study, Group A comprising of patients receiving TELMISARTAN 80mg accounts for 4 ADRs which include 2 cases of Dizziness, 1 case of fatigue and 1 case of headache. Group B comprising of patients receiving TELMISARTAN 40mg + AMLODIPINE 5mg accounts for 3 ADRs which include 2 cases of fatigue and 1 case of headache.

Table 1: Age distribution of the participants of the study

S.No	AGE GROUP	FREQUENCY IN GROUP A (RECEIVING TELMISARTAN 80mg)	FREQUENCY IN GROUP B (RECEIVING TELMISARTAN 80mg + AMLODIPINE 5mg)	TOTAL FREQUENCY
1	40-50	8	3	11
2	50-60	11	8	19
3	60+	11	19	30
			TOTAL	60

Table 2: Changes in the SBP of the patients in Group A receiving Telmisartan 80mg and in Group B receiving Telmisartan 40mg + Amlodipine 5mg during the course of the study

Time line	SBP RANGES (in mm of Hg) in Group A				SBP RANGES (in mm of Hg) in Group B			
	121-130	131-140	141-150	>150	121-130	131-140	140-150	>150
0 week	0	0	10	20	0	0	8	22
8 week	4	18	8	0	11	14	5	0

Table 3: Changes in the DBP of the patients in Group A receiving Telmisartan 80mg and Group B receiving Telmisartan 40mg + Amlodipine 5mg during the course of the study

Time line period	DBP RANGES (in mm of Hg) in Group A				DBP RANGES (in mm of Hg) in Group B			
	71-80	81-90	91-100	>100	71-80	81-90	91-100	>100
Week 0	0	8	22	0	0	4	23	3
Week 8	7	21	2	0	18	12	0	0

Effect of treatment on the mean SBP and DBP of participants in Group A receiving Telmisartan 80mg and Group B receiving Telmisartan 40mg + Amlodipine 5mg during the course of the study.

Table:4 shows that the results of the Paired t-test indicated that the reduction in mean SBP and DBP from baseline to end of study in Group A receiving Telmisartan 80mg was statistically significant ($p < 0.05$). and in Group B receiving Telmisartan 40mg + Amlodipine 5mg was statistically significant ($p < 0.05$)

GROUP A (n = 30)	TIME PERIOD	Mean ± SD	Paired T Test,p-value	GROUP B (n=30)	Mean ± SD	Paired T-Test p - value
SBP	WEEK 0 (Baseline)	154 ± 3.7	0.002*	WEEK 0 (Baseline)	157.3 ± 5.4	0.002*
	WEEK 8	138 ± 5.2		WEEK 8	135.3 ± 5.4	
DBP	WEEK 0 (Baseline)	93.8 ± 3.4	0.001	WEEK 0 (Baseline)	97.2 ± 5.6	0.001*
	WEEK 8	83.8 ± 3.5		WEEK 8	81.3 ± 5.1	

DISCUSSION

The study was conducted in GOVERNMENT GENERAL HOSPITAL, KURNOOL on the outpatients and inpatients of Department of General Medicine to compare the response of hypertensive patients to therapy with high dose Telmisartan monotherapy (30 patients) and low dose combination therapy with Telmisartan-Amlodipine (30 patients).

The study sample consisted of 60 patients who were diagnosed with hypertension and were prescribed either high dose Telmisartan monotherapy(80mg) or

low dose combination therapy with Telmisartan(40mg) and Amlodipine(5mg) by the clinician.

Diuretics and vasodilators in contrast elevate plasma renin levels.[10]

Angiotensin Receptor Blockers (ARB) are first line therapy of Hypertension, and has outstripped the use of angiotensin converting enzyme inhibitors(ACEIs).[8] Pharmacologically ARBs differ from ACEIs,

a. do not interfere with degradation of bradykinin
b. more complete inhibition of AT1 receptor activation, because responses to Ang II generated via alternate pathways and consequent AT1 receptor activation are also blocked.
c. blockade of AT1 receptor mediated feedback inhibition -more angiotensin II produced which acts on AT2 receptor that remain unblocked.[8]

Telmisartan was reported to be preferred by almost 73% of physicians in India as a first-line agent for managing essential hypertension.[11] Telmisartan has a very high lipophilicity and high volume of distribution which offers advantage of good tissue penetration over other sartans.[12] Telmisartan is free from the side effect of dry cough associated with ACEI's and has better tolerability profile[13]. Amlodipine is a long-acting, lipophilic, third generation dihydropyridine (DHP) CCBs.[14] It has high volume of distribution and small diurnal fluctuation in blood level.[4] Combining CCB with other antihypertensives reduces the incidence of oedema occurring due to the use of higher doses of CCB alone.

Drawbacks with Monotherapy

A recently appreciated aspect of RAS inhibition is the presence of alternative pathways capable of producing ang II without any appreciable contribution by ACE. Most antihypertensive agents increase plasma renin activity leading to accumulation of ang I, which in turn facilitate metabolism of ang I into ang II via alternative pathways, most notably chymase activity in cardiac monocytes, vascular smooth muscle cells, and renal mesangial cells; this so-called "ACE escape" can result in a diminished response to drug over time.[15]

The dose of anti-hypertensive agent is often increased if initial mono-therapy does not produce the desired BP-lowering effect. Up-titrating anti-hypertensive dose may improve BP response rates but usually also increase the occurrence of side effects which, in turn, may lead to reduced patient compliance and treatment discontinuation.

Advantages of combination therapy

Since blood pressure is result of several physiological mechanisms, thus an attempt to block one (as in mono-therapy) tends to increase compensatory activity of others. Therefore, two drugs from different classes with complimentary mechanisms of action may result in additional BP control compared with either agent used alone.

combining a renin-angiotensin system (RAS) inhibitor to a Calcium channel blocker appears to be associated with low incidence of CCB-related oedema.[16]. This attenuation of oedema appears to be due to the ability of RAS inhibitors to counteract CCB induced microcirculatory changes, though the exact mechanism remains to be established.[17]

This telmisartan/amlodipine combination has also been demonstrated to be effective in patients at all stages of hypertension, as well as in those with added risk factors including obesity, diabetes, or metabolic syndrome.

This is to be expected due to the complimentary modes of actions of the two drugs. Adding an ARB to CCB therapy should promote arterial and venous dilation by blocking the RAS system and attenuate renal hyperfiltration induced by CCBs.

The combination may be especially appropriate for those with diabetes and/or metabolic syndrome as these medications do not worsen the metabolic complications associated with their etiology.

This study indicates that clinicians can be assured of efficacy and safety of low dose combination than monotherapy. The long-term safety and efficacy profile of the telmisartan/amlodipine combination pill, reduce BP through complementary mechanisms that are synergistic in their BP-lowering effects.

In this study, the fall in mean SBP observed in group B (treated by Telmisartan 40mg + Amlodipine 5mg) was greater than that observed in group A (treated by Telmisartan 80mg). The reduction in SBP observed were 22 vs 16 mm of Hg in group B and group A respectively which is within the range estimated from previous analogous studies.

In this study, 63.3% patients in Group A receiving Telmisartan 80mg had achieved SBP control by the 8th week while 83.3% in Group B receiving Telmisartan 40mg + Amlodipine 5mg had achieved SBP control by 8th week respectively.

In this study, the fall in mean DBP observed in group B (treated by Telmisartan 40mg + Amlodipine 5mg) was greater than that observed in group A (treated by Telmisartan 80mg). The reduction in DBP observed were 16 vs 10 mm of Hg in group B and group A respectively which is within the range estimated from previous analogous studies.

In this study, By the 8th week, 86.6% participants in Group A receiving Telmisartan 80mg had achieved DBP control, and 90% participants in Group B receiving Telmisartan 40mg + Amlodipine 5mg had achieved DBP control. The difference between the two groups was minor as anticipated in previous similar studies.

The results of the Paired t-test indicated that the reduction in mean SBP and DBP from baseline to end of study in Group A receiving Telmisartan 80mg was statistically significant ($p < 0.05$)

The results of the Paired t-test indicated that the reduction in mean SBP and DBP from baseline to end of study in Group B receiving Telmisartan 40mg + Amlodipine 5mg was statistically significant ($p < 0.05$).

In this study, the incidence of ADRs observed in group A (13.3%) receiving Telmisartan 80 mg was found to be higher than that observed in group B (10%) receiving Telmisartan 40mg + Amlodipine 5mg.

The results indicate that the efficacy of Telmisartan 40mg + Amlodipine 5mg low dose combination in achieving BP control (SBP</=140mm of Hg and DBP</=90mm of Hg) is greater than the high dose monotherapy with Telmisartan 80mg (Tables 2 and 3).

Both high dose monotherapy with Telmisartan as well as low dose combination therapy of Telmisartan and Amlodipine had similar tolerability and only a handful of adverse drug reactions were reported in both groups which is a testament to its tolerability.

New findings during this study

Patients with depression exhibit increased sympathetic tone and decreased parasympathetic activity, which not only contributes to an increase (and poor control) of blood pressure, but also may increase the risk of cardiac arrhythmias. Interestingly, the use of serotonin reuptake inhibitors decreases sympathetic activation, although whether antidepressant treatment improves blood pressure control requires additional investigation.[18] Depression is increased among covid affected family members due to loss of beloved ones, indirectly contributing to hypertension recently.

CONCLUSION

In this study, a low dose Telmisartan–Amlodipine combination has demonstrated significantly greater BP reductions for both SBP and DBP compared to high dose mono-therapy of Telmisartan and Amlodipine in the overall study population. This combination is well tolerated with a safety profile consistent with its mono-therapy components. So, in terms of BP control, low-dose combination therapy appears a better therapeutic approach than high-dose mono-therapy for mild to moderate hypertensive patients who failed to achieve BP target on low-dose mono-therapy.

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