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Original Research Article

Study of antihypertensive effect of ramipril alone and in combination with telmisartan

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ABSTRACT

Background: Hypertension is one of the leading causes of the global burden of disease. Hypertension has been associated with increased risk of cardiovascular diseases, including coronary heart disease (CHD), congestive heart failure (CHF), ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease. Majority of the hypertensive population are still either untreated or inadequately treated. Aims and objectives of the study were to compare ramipril alone and in combination with telmisartan as an antihypertensive in mild to moderate hypertension.
Methods: This study was a hospital based prospective, comparative randomized, observational study conducted over a period of one year. The subjects of this study had mild to moderate hypertension selected from outpatient department of department of General Medicine of a tertiary care hospital. For the purpose of this study, equal numbers of subjects were randomly allocated equally between two groups: one group on ramipril alone and the other group on combination of ramipril and telmisartan. Patients were assessed for the blood pressure (BP) reduction during follow-up period of 6-months.
Results: Ramipril alone and in combination with telmisartan, both were associated with significant reduction of systolic BP (SBP), diastolic BP (DBP), and mean BP (MBP) from beginning to the end of study. Combination of ramipril with telmisartan was more effective than ramipril in lowering SBP during 4 to 12 weeks but at the end of study both drug groups were found to be equally effective antihypertensive. Both ramipril alone and in combination with telmisartan were equally effective in lowering DBP and MBP from beginning to end of study.
Conclusions: There was a significant reduction of SBP, DBP, and MBP from beginning to the end of study with both ramipril alone and in combination with telmisartan. Ramipril alone and in combination with telmisartan, both were equally effective antihypertensive for mild to moderate hypertension.

Keywords: ACE inhibitors, ARBs, Hypertension, RAS

INTRODUCTION

Hypertension (HT) is one of the leading causes of the global burden of disease. Hypertension has been associated with increased risk of cardiovascular diseases, including coronary heart disease (CHD), congestive heart failure (CHF), ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease. Majority of the hypertensive population are still either untreated or inadequately treated. Cardiovascular disease risk doubles for every 20-mmHg increase in systolic and 10-mmHg increase in diastolic pressure. Among older individuals, systolic blood pressure (SBP) and pulse pressure (PP) are more powerful predictors of cardiovascular disease than is diastolic blood pressure.[1] Systolic blood pressure tends to rise disproportionately greater in the elderly due to decreased compliance in blood vessels associated with aging and atherosclerosis. Isolated systolic hypertension (sometimes defined as systolic BP >140-160 mm Hg with diastolic BP <90 mm Hg) is largely confined to people older than 60 years of age.[2]

The renin-angiotensin system (RAS) plays a pivotal role in the progression of cardiovascular and renal diseases.[3]

Angiotensin II by its action on angiotensin II type 1 (AT1) receptor leads to vasoconstriction and sympathetic activation, aldosterone secretion, and promotes salt and water retention.[4]

Both angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) are the first line drugs for hypertension and they effectively reduce the risk of cardiovascular and renal events.[5]

The ACE inhibitors inhibit the conversion of angiotensin I to angiotensin II leading to decreased activation of both AT1 and AT2 receptors. Angiotensin II acts on AT1 receptors leading to raised blood pressure (BP), endothelial dysfunction, vascular hypertrophy, inflammation, atherosclerosis, and apoptosis. An important disadvantage of ACE inhibition is reduced activity of the AT2 receptor. In contrast to the AT1 receptor; the AT2 receptor has pro-differentiation, anti-proliferative, and anti-inflammatory properties.[6] ACE inhibitors inhibit bradykinin degradation leading to B2 receptor activation which results in nitric oxide release having vasodilatory and tissue protective effects. Activity of an ACE inhibitor on the angiotensin converting enzyme (ACE) acting as cell surface receptor initiates a signalling cascade resulting in PGI2 generation and additional vasodilatory effects.[7-9] Chronic use of ACE inhibitors has been associated with reactivation phenomena which has been associated with poorer outcomes.[10,11] Cough is the most frequent reason for ACE inhibitor discontinuation.[12]

Telmisartan, an ARB, inhibits actions of angiotensin II by binding with AT1 receptor. ARBs selectively bind with AT1 receptor resulting in higher inhibition of the RAS than ACE inhibitors.[5] In addition, ARBs permit activation of the AT2 receptor by angiotensin II leading to unopposed anti-inflammatory and anti-proliferative effects.[6] As compared to all the other first line drugs for HT, ARBs have highly favourable tolerability profile.[13] Telmisartan is more effective than ramipril as an antihypertensive during the early morning blood pressure surge (EMBPS).[14] Among ARBs, telmisartan is superior to losartan and valsartan in reducing the BP throughout the 24-h period.[15] Due to the long duration of action, telmisartan provides BP control throughout the whole 24-h period at once a day dosing.[16]

Greater BP reduction is achieved if combination of drugs for hypertension with complementary mechanism of action is employed than either drug alone.[17] For the same reason, combination of ACEI and ARB have been found to have greater BP reduction than either drug alone.[18,19] The combination of ACEI and ARB, reduces the chances of escape observed when either one of them is used alone.[20]

Mild hypertension has been defined as DBP within 90-99 mmHg and/or SBP within 140-159 mmHg while moderate hypertension has been defined as DBP within 100-109 mmHg and/or SBP within 160-179 mmHg, respectively.[21]

Most of the studies on antihypertensive agents have been done in western population. Being ethnically different from our Caucasian counterpart, by this study, we want to establish an epidemiological data regarding BP reduction with ramipril alone and in combination with telmisartan in patients having mild to moderate hypertension at our settings. The idea beyond this study is to get an evidence based appropriate drug or drug combination for hypertension.

METHODS

This study was a hospital based prospective, comparative randomized, observational study conducted over a period of one year. The subjects of this study had mild to moderate hypertension selected from outpatient department of department of General Medicine of a tertiary care hospital.

Subjects were selected as per the inclusion and exclusion criteria. The inclusion criteria for this study were subjects of either sex of more than 25 years of age who were newly diagnosed patients, previously diagnosed patients of hypertension who were aware that they have hypertension and were not on any antihypertensive medication and hypertensive patient for less than past 5 years and were on irregular treatment.

The patients were excluded from the study if they had malignant and secondary hypertension, had severe hypertension i.e. systolic blood pressure >180 mm Hg and diastolic blood pressure >110 mm Hg, serum creatinine level >1.5 mg/dl, known hypersensitivity or intolerance to angiotensin converting enzyme inhibitor and angiotensin receptor blockers, uncontrolled hypertension on treatment (e.g., BP >160/100 mm Hg), hemodynamically significant valvular or outflow tract obstruction, simultaneously taking another antihypertensive medication, hepatic dysfunction, significant renal artery disease, significant gastrointestinal or neurological disorder, uncorrected volume or sodium depletion, pregnant and lactating females, and female patients of the child-bearing age group not using medically approved contraceptives, unable to provide written informed consent, major noncardiac illness expected to reduce life expectancy or significant disability interfere with study participation. Written informed consent was taken from every patient before entry in the trial. Simple random sampling was done for the allocation of group. For the purpose of study, equal numbers of patients were randomly allocated equally between two groups.

Drug protocol followed in each group:

- Group A (50 patients) - Tablet ramipril 5 mg orally once a day at morning time (between 8 a.m.-10 a.m.)

- Group B (50 patients) - Tablet ramipril 5 mg+ telmisartan 40 mg orally once a day at morning time (between 8 a.m.-10 a.m.)

Patients were assessed for the changes in the blood pressure with a follow up of over a period of 24 weeks. Patients were assessed at the time of screening (1st visit), then after the 1 week run in period (2nd visit) and then after 1 month (3rd visit), 3rd month (4th visit) and 6th month (last visit). In each assessment visits, both systolic and diastolic blood pressure were measured in the sitting, standing and lying position using a standardized procedure.

All subjects went through thorough history, clinical examination and biochemical investigations. During first visit, subjects were examined completely with due consideration to medical history, family history, socioeconomic history, past history and addiction history. Patients were examined physically to record the BMI, anthropometric measurements, and vital signs. Systemic examination including cardiovascular system, respiratory system, central nervous system and abdominal examination were done. X-ray chest, resting ECG, fundus examination, laboratory examination including hemoglobin, total and differential WBC count, blood sugar, blood urea, serum creatinine, lipid profile and urine examination were done. At subsequent visits, suitability of patient was assessed based on the efficacy of drugs compliance, reporting of any adverse drug reactions and laboratory values including serum creatinine level to continue with the trial.

BP changes from baseline to 24 weeks of study (1st, 4th, 12th and 24th week) were analyzed statistically by using SPSS program. Results were expressed as means±SEM. Chi square test was applied to test the statistical significance. The confidence limit of the study was kept at 95%, hence a "p" value <0.05 indicated a statistically significant association.

RESULTS

The antihypertensive effects of ramipril alone and in combination with telmisartan were compared. Effects of both ramipril alone and in combination with telmisartan were similar and comparable with regards to reduction of systolic BP and diastolic BP. In both ramipril alone and in combination with telmisartan groups, there was significant reduction of SBP, DBP and MBP from beginning to end of study (p<0.001) (Table 1).

In the ramipril-treated group, the mean SBP prior to treatment was 165.0±8.32 mm Hg. After 1st week, 4th week and 12th week, the mean SBP were 158.4±11.8, 151.64±11.23 and 134.88±10.02 mm Hg respectively. At the end of 24th week, the mean SBP was 129.56±9.64 mm Hg. In the ramipril + telmisartan treated group, the mean SBP prior to treatment was 164.40±7.451 mm Hg. After 1st week, 4th week and 12th week, the mean SBP were 157.48±9.159, 147.88±8.518 and 131.52±7.268 mm Hg respectively. At the end of 24th week, the mean SBP was 130.72±6.661 mm Hg. In both ramipril alone and ramipril + telmisartan groups, the reduction in SBP was found to be statistically significant after one week, four weeks, twelve weeks of therapy and end of study when compared with the baseline readings.There was significant difference in the SBP reduction seen between ramipril alone and ramipril + telmisartan group during the period of 4th week to 12th week. No significant difference in the SBP reduction between the two groups was seen at the end of the study (Table 2).

Table 1: Mean SBP, DBP and MBP in all groups at the beginning and end of study.

Duration of Treatment	Ramipril		Ramipril + Telmisartan	
	Mean		Mean	
	Initial	End of Study	Initial	End of Study
SBP	165.00±8.323	129.56±9.641	164.40±7.451	130.72±6.661
	24.689 <0.001 (H.S)		38.096 <0.001 (H.S)	
DBP	98.48±4.34	84.08±4.60	98.32±4.10	83.96±4.47
	19.860 <0.001 (H.S)		18.959 <0.001 (H.S)	
MBP	120.65±4.739	99.240±5.84	120.34±4.68	99.542±4.54
	27.008 <0.001 (H.S)		32.560 <0.001 (H.S)	

In the ramipril-treated group, the mean DBP prior to treatment was 98.48±4.34 mm Hg. After 1st week, 4th week and 12th week, the mean DBP were 93.64±6.21, 90.4±5.32 and 84.68±4.75 mm Hg respectively. At the end of 24th week, the mean DBP was 84.08 ±4.60 mm Hg. In the ramipril+telmisartan treated group, the mean DBP prior to treatment was 98.32±4.10mm Hg. After 1st week, 4th week and 12th week, the mean DBP were 94.88±5.37, 89.68±5.06 and 84.72±4.49 mm Hg respectively. At the end of 24th week, the mean DBP was 83.96±4.47mm Hg. In both ramipril alone and ramipril+telmisartan groups, the reduction in DBP was found to be statistically significant after one week, four weeks, and twelve weeks of therapy and at the end of study when compared with the baseline readings. There was no significant difference in the DBP reduction seen between the two groups during the study (Table 3).

Table 2: Comparison of mean SBP between treatment groups from baseline to 1st week, 4th week, 12th week and end of study (24th week).

Duration of treatment	Value	Ramipril Vs Ramipril + Telmisartan	
Initiation	Mean	165.00±8.323	164.40±7.451
	T-value	0.355	
	P- value	0.724 (N.S)	
1st Week	Mean	158.40±11.822	157.48±9.159
	T-value	0.516	
	P- value	0.608 (N.S)	
4th Week	Mean	151.64±11.239	147.88±8.518
	T-value	2.197	
	P- value	0.033 (S)	
12th Week	Mean	134.88±10.030	131.52±7.268
	T-value	2.331	
	P- value	0.024 (S)	
End of Study	Mean	129.56±9.641	130.72±6.661
	T-value	0.814	
	P- value	0.42 (N.S)	

Table 3: Comparison of Mean DBP between treatment group from initiation to 1st week, 4th week, 12th week and end of study (24th week).

Duration of Treatment	Value	Ramipril Vs Ramipril + Telmisartan	
Initiation	Mean	98.48±4.34	98.32±4.10
	T-value	0.215	
	P- value	0.831 (N.S)	
1st Week	Mean	93.64±6.21	94.88±5.37
	T-value	1.089	
	P- value	0.281 (N.S)	
4th Week	Mean	90.4±5.32	89.68±5.06
	T-value	0.649	
	P- value	0.519 (N.S)	
12th Week	Mean	84.68±4.757	84.72±4.49
	T-value	0.043	
	P- value	0.966 (N.S)	
End of Study	Mean	84.08±4.60	83.96±4.47
	T-value	0.141	
	P- value	0.888 (N.S)	

In the ramipril alone group, the average MBP prior to treatment was 120.65±4.739 mm Hg. After 1st week, 4th week and 12th week, the average MBP were 115.28±6.91, 110.81±6.10 and 101.02±5.90 respectively. At the end of 24th week, the average MBP was 99.21±5.84 mm Hg. In the ramipril+telmisartan treated group, the average mean blood pressure (MBP) prior to treatment was 120.34±4.68. After 1st week, 4th week and 12th week, the average MBP were 115.74±5.71, 109.07±5.57 and 98.04±3.58 mm Hg respectively. At the end of 24th week, the average MBP was 100.37±5.03mm Hg. In both ramipril alone and ramipril+telmisartan groups, the reduction in MBP was found to be statistically significant after one week, four weeks and twelve weeks of therapy and at the end of study when compared with the baseline readings. There was no significant difference in the MBP reductions seen between the two groups during the period of study (Table 4).

Table 4: Comparison of Mean MBP between treatment group from initiation to 1st week, 4th week, 12th week and end of study (24th week).

Duration of Treatment	Value	Ramipril Vs Ramipril + Telmisartan	
Initiation	Mean	120.65±4.739	120.34±4.68
	T-value	0.343	
	P- value	0.733 (N.S)	
1st Week	Mean	115.22±6.87	115.74±5.71
	T-value	0.485	
	P- value	0.630 (N.S)	
4th Week	Mean	110.81±6.10	109.07±5.57
	T-value	1.481	
	P- value	0.1417 (N.S)	
12th Week	Mean	101.02±5.90	100.37±5.03
	T-value	1.057	
	P- value	0.296 (N.S)	
End of Study	Mean	99.240±5.84	99.542±4.54
	T-value	0.322	
	P- value	0.749 (N.S)	

DISCUSSION

In our study, we found that both ramipril alone and ramipril+telmisartan combination are equally effective antihypertensive drugs for mild to moderate hypertension. In another study, ramipril+telmisartan combination was found to be to non superior to ramipril.[22] In mild to moderate hypertension, ramipril and telmisartan individually, both have been found to be equally effective antihypertensive.[23]

In hypertensive patients, addition of an ARB candesartan to the ACEI lisinopril had the same degree of BP reduction as compared to the doubling the dose of lisinopril.[24]

Ramipril + telmisartan combination have been found to be associated with more adverse effects than ramipril. [22]In subjects with symptomatic left ventricular dysfunction combination, ARB plus ACE inhibitor therapy was associated with higher incidences of adverse effects compared with ACEI alone.[25]

This is, in contrast, to findings of some of the previous studies. In a cross-over study, ACEI and ARB combination was found to have superior BP control in hypertensive patients in whom BP was not controlled by ACEI alone. In this study, antihypertensive effects of benazepril were compared with benazepril+valsartan combination.[26] Similarly, the combination of ACEI lisinopril and ARB telmisartan was associated with

higher BP reduction than lisinopril alone.[27] In patients with CHF and reduced left-ventricular ejection fraction, combination of ACEI and ARB had been found to significantly reduce cardiovascular events as compared to ACEI alone.[28]

In type I diabetic patients with diabetic nephropathy, ACEI and ARB combination was superior to ACEI alone for lowering of BP as well as albuminuria.[29]

Dual RAS blockade with an ACEI ramipril and ARB telmisartan have been found to have greater reduction in MBP as compared to ACEI ramipril alone.[22] Similarly, dual RAS blockade with an ACEI lisinopril and an ARB candesartan was associated with higher reduction in PP than lisinopril.[30] In patients having hypertension with diabetes, there was no significant difference in SBP reduction found between lisinopril 40 mg once daily and lisinopril 20 mg in combination with candesartan 16 mg once daily.[31] In this study, significant difference in SBP reduction between ramipril+telmisartan combination and ramipril alone was seen during 4 to 12 weeks. No significant difference in the SBP reduction between two groups was seen at the end of the study. There was no significant difference in reduction of MBP and DBP between two groups was found from beginning to end of study.

CONCLUSION

There was a significant reduction of SBP, DBP, and MBP from beginning to the end of study with both ramipril alone and in combination with telmisartan. Ramipril alone and in combination with telmisartan, both were equally effective antihypertensive for mild to moderate hypertension. Although further studies can be planned to find out the rationale behind the greater reduction in SBP for the period between 4th to 12th week with telmisartan+ramipril combination than with ramipril alone.

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