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Clinical efficacy and safety of telmisartan versus losartan and their effect on lipid profile in stage 1 hypertension: A randomized, double blind, 12 week trial

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Abstract

Aim: The aim of this study was to compare the efficacy and safety of telmisartan and losartan and also to examine their effect on lipid profile in patients of stage 1 hypertension.
Method: Sixty three, stage 1 hypertensive patients were divided randomly into telmisartan and losartan group of 32 and 31 patients respectively. At baseline and 12 weeks, systolic (SBP) and diastolic blood pressure (DBP), blood sugar level (BSL), total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL), very low density lipoprotein (VLDL) and high density lipoprotein (HDL) were measured.
Result: The primary finding of the present study was that telmisartan and losartan significantly decreased SBP and DBP at 12 weeks compared to baseline but there was no significant difference in reduction of blood pressure in between both groups. It was also observed that fasting blood sugar level, serum total cholesterol, triglyceride, VLDL, and LDL decreased significantly and HDL increased significantly ($p < 0.001$) after 12 weeks of treatment in telmisartan group only. No serious adverse effects were reported during the study.
Conclusion: It was observed that only telmisartan and not losartan significantly improved lipid profile at 12 weeks.
Keywords: telmisartan; losartan; lipid profile; stage 1 hypertension; efficacy; safety.

1. Introduction

Hypertension is the most common cardiovascular disorder conventionally defined as a sustained increase in blood pressure ≥ 140 /90 mm of Hg. The prevalence of hypertension varies with advancing age, race, education and many other variables. About sixty to eighty percent of both men and women develop hypertension by the age of 80 years.[1] Elevated arterial pressure causes pathological changes in the vasculature and hypertrophy of the left ventricle. As a consequence, hypertension is the principle cause of stroke, a major risk factor for coronary artery disease and its attendant complications such as myocardial infarction and sudden cardiac death. It is a key contributor to the cardiac failure, renal insufficiency and dissecting aneurysm of aorta.[2] Effective antihypertensive therapy reduces the risk of stroke, cardiac failure and renal insufficiency and subsequently reduces morbidity and mortality rates.

Hypertension and hyperlipidemia commonly coexist. In hypertensive individuals, there is a high prevalence of decreased level of high density lipoprotein (HDL), increased total cholesterol and elevated triglyceride (TG) levels as compared to normotensive individuals.[3] Elevated total cholesterol (TC) levels increase the risk of cardiovascular disease associated with hypertension and dyslipidaemia. When these two conditions coexist, it demands a strict emphasis on dietary and pharmacological therapy to achieve control on both successfully. Contrary to the goal, it is reported that only in 32 % of hypertensive patients; lipid profile is improved, while this percentage falls to eleven for control of both blood pressures (BP) and lipids.[4]

The antihypertensive drugs primarily affect the increased blood pressure without affecting the disordered lipid metabolism that often accompanies hypertension. Angiotensin II receptor blockers (ARBs) are efficient antihypertensive agents that act through inhibition of AT_1 receptors.[5] ARBs have the ability to affect lipid metabolism in a modest but significant way. ARBs improve the overproduction and accumulation of TG in the liver, through mechanisms independent of their hypotensive action in experimental models.[6] Telmisartan is a recently marketed drug and the effect of telmisartan

on various systems is largely undiscovered. Literature showed variable, confusing and inconsistent results about effect of telmisartan on lipid levels. [7-11] Hence, it was considered worthwhile to establish the role of telmisartan on lipid profile and its effect on cardiovascular parameters. Therefore, the study was planned to compare the efficacy, safety and its effect on lipid profile with losartan, which is a well established antihypertensive agent.

2. Methods

Sixty six patients of stage 1 hypertension attending the outpatient hypertension clinic participated in a prospective, randomized, double-blind, comparative 12 week-study approved by Institutional Ethics Committee from February 2011 to October 2012. The study protocol was in accord to the Helsinki declaration.Written informed consent was obtained from each patient before enrolment in the study by explaining the nature of the study to the patients. Patients of either gender in the age group 18- 60 years having blood pressure >140/90 mm Hg newly diagnosed stage 1 hypertensive patients having fasting blood sugar (FBS) level< 110 mg/dl, total cholesterol (TC) levels < 240 mg/dl or triglycerides (TG)<150 mg/dl were included in the study. Patients having stage 2 hypertension, secondary hypertension, on any anti hyperlipidemic therapy, medical illness including endocrine and metabolic diseases, pregnant and lactating women, hepatic or renal dysfunction, regular drinkers or heavy smokers were excluded. Patients having history of hypersensitivity or allergy to telmisartan or losartan were also excluded. Routine investigations like electrocardiogram, serum electrolytes, blood urea, serum creatinine, liver function test were performed to rule out active medical problems in all patients.

Patients were divided randomly into two groups A and B of 33 each. Sample size was calculated by using level of significance 5% and power 80% with a difference of 5 mm Hg in systolic blood pressure and standard deviation 6.75 was taken from a pilot study. The calculated sample size was 30 in each group. So the study sample size was rounded to sixty six (33 patients in each group) considering future rate of dropouts. The study being double-blind, the drugs were identical in formulation, shape, size, weight, texture and packing. Block randomization procedure was used for random allocation of study groups, A and B with blocks of size 4 in equal proportions to ensure uniform allocation ratio (1:1). The randomized treatment allocation sequence was generated by statistician using random number table. The drugs (forty five either of telmisartan or losartan) were handed over in identical plastic containers to a third person who was not directly involved in this study. This person labeled the containers according to the random allocation sequence of patients with drugs provided. The code of this random allocation sequence was retained in a sealed envelope and was opened only after completion of the study. The patients as well as the investigators were unaware of the treatment administered. Drugs were issued to patients for duration of forty-five days at a time. Patients were asked to bring the unused drugs and container during the follow-up and were again issued a new supply of the drugs for forty-five days. Compliance of the patient was checked by counting the unused number of tablets. Ninety percent consumption was considered to be compliant. The returned tablets were discarded. Drugs were decoded at the end of trial. Group A received telmisartan 40 mg once daily and group B received losartan 50 mg once daily. Same doses were maintained throughout the study. Patients were not stabilized before enrolment in the study as they were satisfying our main inclusion criteria. No comorbid condition was observed in patients during the study period. After study period was over, subjects were handed over to respective physicians.

Blood pressure measurement, fasting blood sugar levels, lipid profile, blood urea, serum creatinine, serum electrolytes, liver function tests and kidney function test were done at baseline and were repeated at 12 weeks. The diagnosis of essential hypertension was made by the physician based on two measurement of blood pressure on two different occasions using auscultatory method. The sphygmomanometer was calibrated and blood pressure was recorded in right arm in sitting position for every patient by same sphygmomanometer and by the same investigator. Fasting Blood Sugar (by GOD/POD method), serum TC, serum TG, serum high density lipoprotein (HDL) were quantitatively estimated in the laboratory of department of biochemistry using semi-autoanalyser, TRANSASIA, ERBA, CHEM-5- PLUS[12-15] while serum very low density lipoprotein (VLDL) and serum low density lipoprotein (LDL) were calculated by Friedwald formula.[16] General clinical safety was monitored by vigilant follow-up of patients for treatment of emergent adverse events, if any, and recorded in the case report form. Patients with adverse drug reaction were treated appropriately by the physician in medicine OPD.

2.1 Data Analysis

Results were expressed as mean (SD). Group differences were ascertained by unpaired‘t’ test. Difference within group was compared by paired‘t’ test or ANOVA followed by Tukey’s post-hoc test. Two-tailed p values of less than 0.05 were adjudged statistically significant. Graph Pad Prism Version 5.00 software was used for analysis.

3. Results

A total of sixty-six patients were randomized and allocated to the treatment, out of which sixty-three patients completed the study according to the protocol. Three patients, one in telmisartan group and two in losartan group lost to follow up at the end of second week of the study. The percentage of male patients was more than female patients, 81.25% in telmisartan group and 77.42% in losartan group. The mean age, height, weight, blood pressure, fasting blood sugar and lipid profile of the patients in telmisartan group and losartan group were similar and there was no significant difference in both groups (table1). The antihypertensive action was measured by decrease in systolic and diastolic blood pressure. It was observed that there was a significant decrease in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 6 and 12 weeks in telmisartan group as well as losartan group (table 2).

We also observed that fasting blood sugar level, serum total cholesterol, triglyceride, VLDL, and LDL decreased significantly and HDL increased significantly ($p < 0.001$) after 12 weeks of treatment in telmisartan group only (table no 3). No significant difference was observed in SGOT, SGPT, blood urea serum bilirubin, alkaline phosphatase, serum creatinine, serum Na^+ and serum K^+ between baseline to 12 week within telmisartan group as well as losartan group. No drug-related adverse events occurred in telmisartan group. Mild headache was reported in one patient in losartan group. No serious adverse effects were reported during the study.

Table 1: Baseline BP, blood sugar and lipid profile of patients

Parameter	Telmisartan group(n=32)	Losartan group (n=31)	P value
SBP (mmHg)	151.8(5.34)	149.8 (4.65)	0.129
DBP (mmHg)	92.44 (3.202)	93.55 (3.25)	0.177
FBSL (mg/dl)	89.09(7.84)	86.58(8.152)	0.217
TC (mg/dl)	165.9(14.17)	164.3(15.05)	0.656
TG (mg/dl)	123.9(13.27)	120.5(16.55)	0.372
VLDL (mg/dl)	24.78(2.65)	24.10(3.31)	0.372
HDL (mg/dl)	46.56(4.91)	45.23(5.749)	0.324
LDL (mg/dl)	94.57(16.40)	94.94(16.98)	0.930

Values are expressed in mean (SD), unpaired 't' test. Abbreviations SBP- systolic blood pressure, DBP- diastolic blood pressure, FBSL- Fasting blood sugar level, TC- total cholesterol, TG- Triglycerides, VLDL- very low density lipoprotein, HDL- High density lipoprotein, LDL – Low density lipoprotein.

Table 2: Effects of telmisartan and losartan on SBP and DBP after 6 and 12 weeks

Parameters	Telmisartan group (n=32)			p value (ANOVA)
	Baseline	6 week	12 week	
SBP (mmHg)	151.8 (5.35)	120.8(5.61)***	119.9(3.57)***	<0.0001
DBP (mmHg)	92.9(3.13)	81.3(3.28)***	80.7(2.19)***	<0.0001
	Losartan group (n=31)			
SBP (mmHg)	149.80(4.66)	117.48(5.03)***	119.16(3.53)***	<0.0001
DBP (mmHg)	93.55(3.25)	80.52(3.72)***	80.97(2.68)***	<0.0001

Values are expressed in mean(SD),*** p<0.001(baseline vs 6 weeks and baseline vs 12 weeks) ; repeated measure ANOVA with Tukey's post hoc test. SBP- systolic blood pressure, DBP- Diastolic blood pressure

Table 3: Effect of telmisartan and losartan on blood sugar and lipid profile

	Telmisartan (n=32)		losartan (n=31)	
	Baseline	12 weeks	Baseline	12 weeks
FBSL (mg/dl)	89.09(7.84)	82.50(6.43)***	86.58(8.15)	87.26(9.51)
TC (mg/dl)	165.9(14.17)	152.5(12.24)***	164.3(15.05)	162.7(13.54)
TG (mg/dl)	123.9(13.27)	116.1(13.57)***	120.5(16.55)	118.5(15.72)
VLDL (mg/dl)	24.78(2.65)	23.22(2.21)***	24.10(3.31)	23.71(3.14)
HDL (mg/dl)	46.56(4.91)	49.44(4.94)***	45.23(5.74)	45.26(5.77)
LDL (mg/dl)	94.57(16.40)	79.88(15.20)***	94.94(16.98)	93.77(15.84)

Values are expressed as mean(SD); paired t test *** p <0.001 compared to baseline. Abbreviations FBSL- Fasting blood sugar level, TC- total cholesterol, TG- Triglycerides, VLDL- very low density lipoprotein, HDL- High density lipoprotein, LDL – Low density lipoprotein

Table 4: Changes in BP, blood sugar and lipid profile from baseline to 12 weeks in telmisartan and losartan groups

Parameters	Change from baseline to 12 weeks	
	Telmisartan (n=32)	Losartan (n=31)
SBP (mmHg)	31.81(5.43)	30.65(6.05)
DBP (mmHg)	12.19(3.39)	12.58(4.17)
FBSL (mg/dl)	-6.59(5.87)***	0.68(5.83)
TC (mg/dl)	-13.38(7.03)***	-1.52(4.77)
TG (mg/dl)	-7.78(4.70)***	-1.94(7.09)
VLDL (mg/dl)	-1.56(0.94)***	-0.39(1.42)
HDL (mg/dl)	2.86(2.18)***	0.03(3.66)
LDL (mg/dl)	-14.69(6.77)***	-1.16(4.93)

Values are expressed as mean(SD); unpaired t test ***p<0.001. Abbreviations SBP- systolic blood pressure, DBP- diastolic blood pressure, FBSL- Fasting blood sugar level, TC- total cholesterol, TG- Triglycerides, VLDL- very low density lipoprotein, HDL- High density lipoprotein, LDL – Low density lipoprotein.

4. Discussion

The ARBs and/or ACEI alone or in combination with calcium channel blocker or with thiazide diuretic are the cornerstone of hypertensive management. ARBs are preferably used to treat hypertension due to lesser side effects and good compliance.[17-20] Hence, this study was planned to compare the effect of newer and more recently market introduced telmisartan with well-established and time tested losartan on their efficacy, safety and metabolic parameters.

The primary finding of the present study indicates that in patients with stage I hypertension, telmisartan and losartan therapy provides significant antihypertensive effect but there was no significant difference in reduction of blood pressure, between both groups suggesting that both drugs are equally efficacious as far as antihypertensive action is concerned.(table 4) The result of this study is in agreement with previously published study showing no significant difference in blood pressure levels between telmisartan and losartan group.[21] A meta-analysis of titration to response studies showed that telmisartan is superior to losartan in controlling SBP and DBP during the last 6 hour of 24 hour dosing interval and this superior reduction in 24-hour mean SBP and DBP with telmisartan may be due to the different pharmacologic effect of the ARBs because of their different chemical structures and their different pharmacokinetic properties and also partly due to its active form and longer duration of action whereas losartan needs to be converted into active metabolite.[22-24]

One of the major finding of this study indicates that telmisartan significantly decreases the fasting blood sugar levels at 12 weeks while losartan had no effect on reduction of fasting blood sugar levels. (table 4) This is similar to other studies which have shown that treatment with telmisartan (40mg) results in a significant improvement in glucose metabolism in insulin resistant subjects with a predominant improvement in beta cell functions.[25] Also, blockade of angiotensin II type I receptors per se, can promote adipocyte differentiation which may contribute to the anti-diabetic effect.[26] This discrepant result for the effect of telmisartan and losartan treatment on glucose metabolism suggests that telmisartan has pleiotrophic effect on glucose metabolism in a manner independent of the angiotensin II receptor antagonist effect. Telmisartan functions as a partial agonist of PPAR-γ, while other commercially available ARBs do not have any effect on PPAR-γ activity.[27,28] Many studies have shown that PPAR-γ plays an important role in regulation of carbohydrate and lipid metabolism which can improve insulin sensitivity. This effect may be related to the insulin sensitizing effects of telmisartan in this study. On the other hand, recent studies have shown that telmisartan ameliorates mitochondrial energy metabolism in skeletal muscle and enhance glucose uptake in the adipocytes accompanied by increase in GLUT4 expression.[29-31] This pharmacological profile might be involved in the strong insulin sensitizing effect of telmisartan. Also, telmisartan exhibits the highest partition co-efficient reflecting high lipophilicity and extensive penetration into target tissue and organs.[32]

In the treatment of hypertension, metabolic influences of antihypertensive drugs appear to be important, especially in their long term use. It is thought that ARBs do not affect lipid metabolism. A number of large scale clinical trials have demonstrated that ARBs prevent the new onset diabetes more effectively than other classes of drugs, such as calcium channel blockers and beta blockers.[33, 34,17] Telmisartan showed a better improvement on most lipid indices, like increase in HDL and decrease in TC, TG, VLDL and LDL than losartan. One of the possible explanations for such an improvement with telmisartan could be that it acts as a partial PPARγ agonist and has more favorable effect on glucose and lipid parameters than the other ARBs. PPARγ regulates lipid metabolism and therefore reduces TG and LDL levels.[35] Also dyslipidaemia may activate angiotensin II induced endothelial injury and lipid peroxidation via an AT1 receptor-

mediated mechanism.[36] Till date many clinical studies have focused on the metabolic effects of telmisartan and losartan. However, results obtained to date, including those of the present study are coherent. There are still controversial results dealing with the effect of telmisartan on lipid profile.[7-10] The cholesterol lowering effect of telmisartan caused by inhibition of cholesterol absorption and advocated the co-treatment of telmisartan and statins, which act by inhibition of cholesterol synthesis, as it may be useful for synergistically lowering cholesterol in hypertension.[11]

5. Conclusion

The results of present study are an important step to understand in a better way the clinical efficacy of telmisartan especially in hypertensive Indian population. In conclusion, telmisartan and losartan, both offer equiefficacious antihypertensive effect but telmisartan offers significant reduction in blood sugar level and beneficial effects on lipid profile than losartan. Therefore, telmisartan may be preferred over losartan in patients suffering from stage 1 hypertension.

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Conflicts of Interests: None

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