Research Paper

Efficacy and Tolerability of Olmesartan, Telmisartan, and Losartan in Patients of Stage I Hypertension: A Randomized, Open-label Study

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Abstract

Objectives: To compare the efficacy and tolerability of losartan, telmisartan, and olmesartan as antihypertensive agents and evaluate and compare their effects on lipid profile and blood glucose. **Materials and Methods:** This was a randomized, open-label, parallel-group, comparative study conducted in sixty patients of Stage I hypertension. The eligible patients were randomly allocated into three treatment groups: (1) Tablet olmesartan (20 mg), (2) Tablet telmisartan (40 mg), and (3) Tablet losartan (50 mg). Blood pressure (BP) was assessed at an interval of 2 weeks for 3 months. Fasting blood glucose (FBG) and lipid profile were estimated at baseline and then at 12 weeks. **Results:** Olmesartan and telmisartan were more efficacious than losartan in reducing diastolic BP (DBP). There was a statistically significant decrease in mean blood glucose level ($P < 0.02$) after 12 weeks of treatment in telmisartan group when compared to baseline. Serum total cholesterol, triglycerides, and low-density lipoproteins decreased significantly after 12-week treatment with olmesartan and telmisartan. **Conclusions:** The most efficacious drug in reducing BP is Olmesartan whereas telmisartan and losartan show equal efficacy. Telmisartan shows the most favorable effects on FBG and lipid profile.

Keywords: Angiotensin II receptor blockers, peroxisome proliferator-activated receptor-gamma, systolic blood pressure

Introduction

Hypertension increases the risk of cardiovascular diseases such as coronary heart disease (CHD), congestive heart failure, cerebrovascular events, renal failure, and peripheral arterial disease.[1] The prevalence of hypertension in India is on the rise with 25% of urban and 10% of rural population being affected with it.[2] The purpose of antihypertensive treatment is to reduce morbidity and mortality associated with cardiovascular and cerebrovascular events resulting from hypertension.[1] Various classes of drugs are being used in the treatment of hypertension such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers, and β-adrenergic blockers.[3] ARBs are one of the first-line drugs for the treatment of hypertension. ARBs are being preferred because they are effective in reducing blood pressure (BP) with good tolerability profile, and convenient once a day dosing.[4] Losartan was the first marketed ARB that has shown relatively ineffective control of BP throughout the day.[5] Subsequently, in 1998, telmisartan was approved by the Food and Drug Administration (FDA), and it offers the advantage of a long plasma half-life of 24 h and improves insulin sensitivity and lipid profiles.[6] Olmesartan medoxomil was approved by FDA in April 2002. It is also shown to improve BP and lipid levels similar to telmisartan.[7]

Various studies have demonstrated the difference in antihypertensive efficacies among ARBs.[8] Although previous

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studies have compared the antihypertensive efficacy of ARBs on the basis of cuff BP change, such comparisons have largely been against a single member of this group. Hypertension and dyslipidemia often coexist and are well-established risk factors for cardiovascular diseases.[9] Very few studies have directly compared losartan, telmisartan, and olmesartan for efficacy, safety, and effect on metabolic parameters such as lipid profile and blood glucose. At the same time, data supporting the same in Indian population are not substantial. There is paucity of studies showing the effect of ARBs on lipid profile in Indian population.

Therefore, the present study was planned in patients of Stage I hypertension with the objectives to compare the efficacy and tolerability of losartan, telmisartan, and olmesartan as antihypertensive and to evaluate and compare the effects of losartan, telmisartan, and olmesartan on lipid profile and blood glucose.

Materials and Methods

The present study was approved by the Institutional Ethics Committee and carried out in accordance with Good Clinical Practice guidelines and the ethical principles as mentioned in the Declaration of Helsinki. This was a randomized, open-label, parallel-group, comparative study conducted in sixty patients of Stage I hypertension carried out from January 2013 to September 2014. Patients were recruited from the medicine outpatient department (OPD) of a tertiary care hospital. Newly diagnosed patients of Stage I hypertension of either gender with age >18 years, willing to participate, and ready to give written informed consent were included in the study.

Patients suffering from diabetes, abnormal liver or kidney function, or any other systemic illness and taking other concomitant medication including antihypertensive medication were excluded from the study. Pregnant and lactating women were also excluded from the study.

Change in sitting cuff diastolic BP (DBP) from baseline to 12 weeks was taken as primary endpoint. Secondary endpoints were change in sitting cuff systolic BP (SBP), change in fasting blood glucose (FBG) FBG level (FBGL), and serum lipids from baseline to 12 weeks.

Tolerability profile of the drugs was also studied.

Study procedure

Patients attending medicine OPD were screened by the physician. For confirmation of diagnosis of hypertension, at least 3 sets of readings were taken on three consecutive days.[10] Patients of Stage I hypertension as diagnosed by the physician (SBP 140–159 mmHg and DBP 90–99 mmHg according to JNC–7 classification)[11] and those who met the inclusion criteria were briefed about the study. Patient information sheet was given to all prospective participants, and written informed consent in vernacular language was obtained from patients willing to participate. Subject confidentiality was maintained throughout the study. A detail medical history was obtained and physical examination performed. Liver function tests (LFTs), kidney function tests (KFTs), FBG, and lipid profile were estimated to check the eligibility of the patients to participate in the study and recorded in the case report form (CRF).

The eligible patients were randomly allocated into the following three treatment groups using computer-generated table of random numbers:

- Group 1: Tablet olmesartan (20 mg once a day)
- Group 2: Tablet telmisartan (40 mg once a day)
- Group 3: Tablet losartan (50 mg once a day).

All the patients were given the respective tablets for 2 weeks and were asked to come for follow-up after 2 weeks. Subsequently, BP was assessed at the interval of 2 weeks for a period of 3 months. Adverse event, if any, was recorded in the CRF. The patient was asked to bring the empty packets of tablets during follow-up visits to check the adherence. Ninety percent consumption was considered to be adequate adherence. After completion of 3 months, LFT, KFT, FBG, and lipid profile were repeated.

Calculation of sample size

Sample size was calculated for 5% α and 80% power. A difference of 6 mmHg in diastolic blood pressure, assuming a standard deviation of 8 was considered for calculation. The calculated sample size was 16 in each group. The study sample size was rounded to sixty (20 patients in each group) considering the rate of dropouts and noncompliance.

Statistical methods

The reduction in BP within each group was analyzed at 2 weeks, 4 weeks, 8 weeks and at 12 weeks using the repeated measures analysis of variance (ANOVA) followed by Tukey's post hoc test. For analysis of FBG and lipid profile before and after treatment in each group, the paired 't' test was used. The intergroup analysis was done using the one-way ANOVA followed by Tukey's post hoc test. Baseline data were analyzed using the one-way ANOVA (parametric data), Kruskal-Wallis (non-parametric data) and Chi- square (nominal data) tests.

Results

A total of 87 patients were screened for participation in the study. Of these, sixty patients satisfied the inclusion criteria and were randomized into three groups of twenty each to receive either olmesartan or telmisartan or losartan. Out of sixty patients of newly diagnosed Stage I hypertension, 57 patients completed the study as per protocol with regular follow-up [Figure 1]. Three patients were lost to follow-up; one in telmisartan group, two in losartan group.

Baseline demographics

Baseline demographic and clinical characteristics of patients receiving olmesartan, telmisartan, and losartan were compared

Table 1: Baseline demographic data and clinical characteristics of hypertensive patients in different groups

Characteristics	Olmesartan (*n*=20)	Telmisartan (*n*=19)	Losartan (*n*=18)	*P*
Age (years)	46.2 (8.66)	48.26 (9.88)	49.94 (9.84)	0.58
Gender[$]				
Men	13	12	12	
Women	7	7	6	
DBP	95.05 (2.20)	94.53 (2.65)	93.44 (2.45)	0.14
SBP	147.38 (5.80)	148.8 (6.02)	149.9 (3.48)	0.48
FBGL	87.85 (12.74)	92.80 (11.84)	89.50 (11.82)	0.91
TC	160.6 (6.38)	165.9 (7.58)	158.6 (7.39)	0.07
TG	124.9 (7.62)	120.7 (8.72)	120.8 (7.27)	0.49
VLDL	23.67 (2.63)	24.20 (3.13)	24.39 (2.83)	0.72
HDL	47.70 (5.36)	45.84 (5.17)	47.78 (5.45)	0.46
LDL	87.54 (5.99)	94.62 (8.17)	87.30 (7.91)	0.14

Values are expressed as mean (SD); One-way ANOVA test. [$]Chi-square test - comparing olmesartan with telmisartan, telmisartan with losartan, and losartan with olmesartan was used to compare between different groups. BP measured in mmHg and lipid profile in mg/dl. FBGL=Fasting blood glucose level, TC=Total cholesterol, TG=Triglycerides, VLDL=Very low- density lipoprotein, HDL=High- density lipoprotein, LDL=Low- density lipoprotein, DBP=Diastolic blood pressure, SBP=Systolic blood pressure, SD=Standard deviation, BP=Blood pressure

Table 2: Effect of olmesartan, telmisartan, and losartan on diastolic and systolic blood pressure in hypertensive patients

Drug	Parameters	Baseline	2 weeks	4 weeks	8 weeks	12 weeks
Olmesartan (*n*=20)	DBP	95.05 (2.15)	85.90 (3.31)*	84.86 (4.07)*	83.71 (6.07)*	81.24 (5.30)*
	SBP	148.3 (6.07)	136.5 (6.22)*	135.7 (6.27)*	133.2 (7.49)*	131.0 (8.50)*
Telmisartan (*n*=19)	DBP	94.53 (2.65)	87.37 (3.59)*	86.32 (5.38)*	85.16 (4.72)*	82.53 (5.99)*
	SBP	148.8 (6.02)	140.4 (6.88)*	140.4 (7.54)*	138.6 (8.22)*	137.1 (8.28)*
Losartan (*n*=18)	DBP	93.44 (2.45)	88.78 (4.60)*	87.33 (5.05)*	87.67 (2.84)**	86.11 (5.15)**
	SBP	149.9 (3.84)	143.00 (5.54)*	142.00 (5.41)*	141.4 (5.81)**	138.7 (5.61)**

Values are expressed as mean (SD), repeated measures ANOVA was used followed by Tukey's *post hoc* test for comparison, *P<0.001, **P<0.0001 when compared with baseline value, BP measured in mmHg. DBP=Diastolic blood pressure, SBP=Systolic blood pressure, SD=Standard deviation, BP=Blood pressure

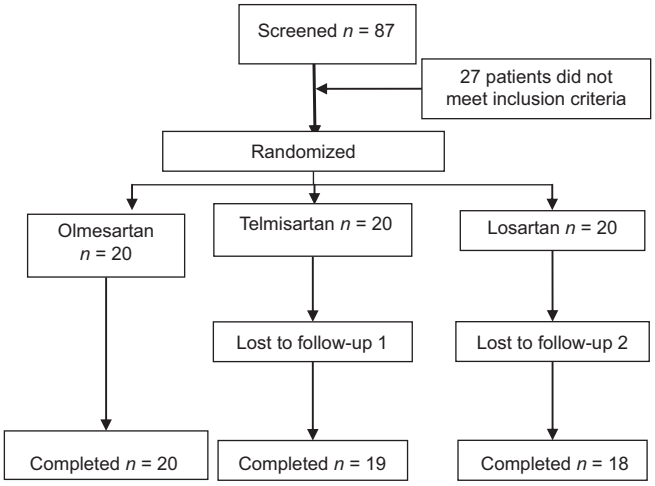

Figure 1: Study flowchart

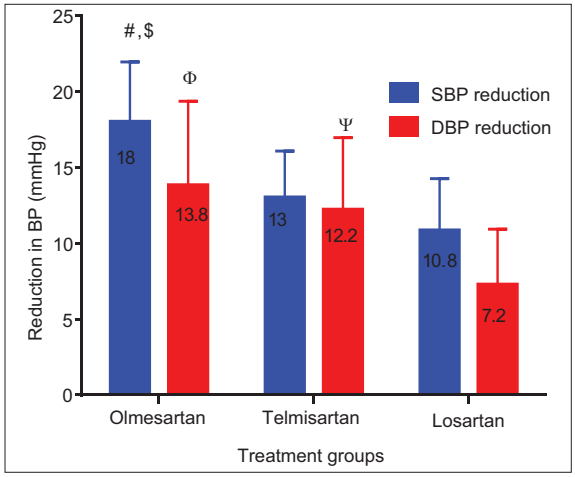

Figure 2: Comparison of reduction in diastolic and systolic blood pressure in treatment groups after 12 weeks. # $P < 0.0001$ when compared with losartan group; $ $P < 0.0001$ when compared with telmisartan group; Φ $P < 0.001$ when compared with losartan group; Ψ $P < 0.01$ when compared with losartan group

and found to be comparable with respect to the demographic and clinical parameters [Table 1].

The reduction in cuff DBP after treatment with olmesartan, telmisartan, and losartan was apparent within 2 weeks. The reduction in diastolic BP and systolic BP were found to be statistically significant at 2, 4, 8, and 12 weeks of therapy in all the three groups when compared with the baseline readings [Table 2].

Efficacy of olmesartan, telmisartan, and losartan in reducing SBP and DBP were assessed by comparing the effects of these drugs after 12 weeks of treatment, taking into consideration the change from baseline values of this parameter, and it was

observed that there was significant difference in reduction of SBP between olmesartan and telmisartan group ($P < 0.0001$) and between olmesartan and losartan group ($P < 0.0001$). However, there was no significant difference in reduction of SBP between telmisartan and losartan group.

Similarly, statistically significant difference was observed in reduction of DBP between olmesartan and losartan group ($P < 0.001$) and between telmisartan and losartan group ($P < 0.01$). However, there was no significant difference between olmesartan and telmisartan groups [Figure 2].

There was statistically significant decrease in mean blood glucose level ($P < 0.02$) after 12 weeks of treatment only in telmisartan group which was not seen in olmesartan and losartan when compared to baseline. However, it was observed that serum total cholesterol (TC), triglycerides (TGs), and low-density lipoproteins (LDL) decreased significantly, and there was no effect on very low-density lipoprotein (VLDL) and high-density lipoproteins (HDL) after 12 weeks treatment with olmesartan and telmisartan.

There was no statistically significant difference in serum TC, TGs, LDL, VLDL, and HDL after 12-weeks treatment with losartan.

Tolerability

Overall, all the three study drugs were well tolerated. No serious adverse events related to treatment were reported. The percentage of patients experiencing adverse events considered to be related to treatment was 5% in the olmesartan and 5.2% in telmisartan group [Table 3].

Table 3: Adverse events in treatment groups

Adverse events	Olmesartan ($n=20$)	Telmisartan ($n=19$)	Losartan ($n=18$)
Headache	1	-	-
Dizziness	-	1	-
Total, *n* (%)	1 (5)	1 (5.2)	0

Table 4: Comparison of changes in blood glucose and lipid profile from baseline to 12 weeks in treatment groups

Parameters	Olmesartan	Telmisartan	Losartan
FBGL	2.45 (0.43)	3.73 (0.88)	−1.11 (0.03)
TC	12.75 (2.12)[a]	8.89 (2.65)	0.83 (0.07)
TG	5.55 (0.46)[b]	8.94 (1.01)[c]	−0.05 (0.01)
VLDL	−0.02 (0.01)	0.18 (0.02)	0.12 (0.03)
HDL	0.60 (0.07)	−0.94 (0.02)	0.05 (0.02)
LDL	8.15 (1.86)[$]	14.65 (1.88)[#,¥]	0.21 (0.06)

Values are expressed in mg/dl as mean (SD); One-way ANOVA with Tukey's *post hoc* test, [a]$P<0.01$ when compared with losartan group, [b]$P<0.05$ when compared with losartan group, [c]$P<0.001$ when compared with losartan group, [#]$P<0.05$ when compared with olmesartan group, [$]$P<0.05$ when compared with losartan group, [¥]$P<0.0001$ when compared with losartan group. FBGL=Fasting blood glucose level, TC=Total cholesterol, TG=Triglycerides, VLDL=Very low- density lipoprotein, HDL=High- density lipoprotein, LDL=Low- density lipoprotein, SD=Standard deviation

Discussion

The principal finding of our study indicates that in patients with Stage I hypertension, treatment with olmesartan, telmisartan, and losartan provided significant antihypertensive effect at 2, 4, 8, and 12 weeks. This is consistent with the findings from previous studies.[5,12,13] In our study, there was significant difference in reduction of cuff DBP, between olmesartan and losartan group and between telmisartan and losartan group. It indicates that olmesartan and telmisartan is more efficacious than losartan in reducing cuff DBP. These observations are in line with the findings of previous studies.[14] Nakayama *et al*. showed that olmesartan, at oral dose of 20–40 mg once daily, was effective, safe, and more efficacious than losartan for hypertension (50–100 mg once daily).[15] The characteristic effect of telmisartan in decreasing the diastolic BP may be related to its long half-life.[12] The greater efficacy of olmesartan in reducing trough cuff DBP may be related to its relatively long half-life of 12–18 h.[5,16] The half-life of losartan is 2 h and that of its active metabolite (EXP3174) is 4–5 h. Since a longer half-life is associated with a longer duration of action, this difference in pharmacokinetics may partially explain the differences in efficacy among these three ARBs. The long half-life of drug such as olmesartan may minimize the effect of missed or delayed dosing of medication.[12] MacMahon *et al*. reported that a reduction in DBP of 5 mmHg is associated with reductions of at least 21% in the incidence of CHD and at least 34% in the incidence of stroke.[17] Significant differences in DBP reduction among these three ARBs noted in our study may be of clinical value. However, there was no significant difference in the reduction of cuff DBP between olmesartan and telmisartan group suggesting that both the drugs are equally efficacious in reducing DBP. Arao *et al*. found no difference between olmesartan and telmisartan group with respect to the antihypertensive effect on the BP.[18] Olmesartan shows high selectivity and strong binding to AT1 receptors while telmisartan has been reported to have a longer residence time on AT1 receptors that contributes to a more sustained antihypertensive effect.[19] In our study, there was significant difference in reduction of SBP between olmesartan and telmisartan group and between olmesartan and losartan group. Our findings are consistent with findings from previous studies.[20] In our study, telmisartan significantly reduced the FBGLs at 12 weeks which was not seen with olmesartan and losartan [Table 4]. Previous studies have also shown that telmisartan (40 mg) once daily results in a significant improvement in glucose metabolism in insulin-resistant subjects with improvement in beta-cell function.[6] Blockade of angiotensin II receptor can promote adipocyte

differentiation and this may contribute to the antidiabetic effect.[21] Several clinical trials have demonstrated that ARBs prevent the new-onset diabetes more effectively than other classes of antihypertensive drugs.[11] However, among ARBs, only telmisartan has blood glucose-lowering effect, indicating that telmisartan has pleiotropic effect on glucose metabolism independent of the angiotensin II receptor antagonist effect.[22] Recently, telmisartan has been shown to function as a partial agonist of peroxisome proliferator-activated receptor-gamma (PPAR-γ) while other ARBs did not have effect on PPAR-γ activity.[6] Many studies have shown that PPAR-γ plays an important role in regulation of carbohydrate and lipid metabolism and that activation of PPAR-γ can improve insulin sensitivity.[23] Results of our study indicated that telmisartan significantly reduced serum TGs and LDL cholesterol when compared with losartan. Telmisartan significantly reduced LDL cholesterol when compared with olmesartan. Observations of our study also showed that olmesartan significantly decreased serum TG, TC, and LDL cholesterol when compared with losartan. However, the reduction of serum TG is not significant in telmisartan group when compared with olmesartan group. Telmisartan activates PPAR-γ, which regulates lipid metabolism. Other mechanisms contributing to the lipid-lowering action of telmisartan could be high lipophilicity and structural differences of telmisartan as compared with other ARBs.[24] Akyürek *et al*. performed a study to determine the metabolic effects of olmesartan in newly diagnosed hypertensive patients. It was reported that TG, TC, FBG, and LDL levels were significantly reduced at the end of 3 months' treatment with olmesartan. However, olmesartan did not produce any significant increases in serum PPAR-γ transcription-factor concentration.[25]

The results of our study show that olmesartan is the most efficacious in reducing BP in Stage I hypertensive patients. Telmisartan has favorable effects on lipid profile. Hence, telmisartan can be the preferred ARB in such patients. However, long-term studies are needed to confirm this effect. In addition, telmisartan lowers blood glucose levels and whether this blood glucose-lowering effect of telmisartan proves to be beneficial in diabetic patients with hypertension needs to be evaluated. The three ARBs have good tolerability profile.

Conclusions

Olmesartan and telmisartan are equally efficacious in reducing DBP whereas losartan is least efficacious. Olmesartan, when compared to telmisartan and losartan is more efficacious in reducing SBP whereas telmisartan and losartan are equally efficacious. Telmisartan shows the most favorable effects on FBG and lipid profile.

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Conflicts of interest

There are no conflicts of interest.

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