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# A Comparative Study of Tolerability of Losartan versus Atenolol in Essential Hypertension and Their Effect on Lipid Profile

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## Abstract

Hypertension is a vascular disease entity that is a common problem occurring worldwide, characterized by sustained elevated blood pressure. Losartan and atenolol are two medications that are commonly used in hypertensive patients. However, the mechanism of tolerability their effect on lipid profile is not clearly described. Thus, the aims of this study were to study the tolerability of losartan with atenolol in patients with hypertension and the changes in lipid profile on treatment. This research was a prospective, open-label, parallel-group, comparative study conducted in the medicine out-patient department (OPD), where 100 patients aged 40-60 years with newly diagnosed mild and moderate hypertension. We classified patients randomly into two groups, losartan, and atenolol (50 patients of each). Patients were recruited for a period of 6 months and were called for follow-up visits at the third and sixth months. In this study mean age of the patients was 52.72 years. Our study observed that baseline systolic (P=0.704), as well as diastolic blood pressure (BP) (P=0.324), was comparable between both groups. Both systolic (P=0.125), as well as diastolic BP (P=0.108) at 6-months, was comparable between both groups. It was observed that mean total cholesterol levels were comparable between both groups at baseline (P=0.665). Moreover, adverse effects were observed more commonly in group atenolol, headache being the most common followed by dizziness and palpitation. Our study observed that both losartan and atenolol are equally effective in long- term reduction of blood pressure. Additionally, losartan also significantly improved lipid profile.

Keywords: Losartan, Atenolol, Hypertension, Lipid Profile, Tolerability

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## Introduction

Hypertension as a vascular disease entity is the common problem occurring in the general population, characterized by sustained elevation of blood pressure (BP).[1] Hypertension is one of the leading causes of the global burden of disease. Elevated BP affects more than one billion individuals and expected to increase to 1.56 billion people by 2025.[2]

According to the report of the joint national committee (JNC VIII) for detection and treatment of high BP, hypertension is defined as a clinical state where the systolic BP is above 139 mmHg and diastolic BP above 89 mmHg respectively.[3] Several risk factors may contribute to its development, including age, gender, weight, physical activity, smoking, family history, diabetes mellitus, renal dysfunction, peripheral resistance vessel tone, endothelial dysfunction, autonomic tone, insulin resistance, and neurohumoral factors.[4,5] Hypertension is known to be associated with alterations in lipid metabolism. It has also been documented that presence of dyslipidemia substantially worsens the prognosis in hypertensive patients.[6]

Several classes of antihypertensive agents have been in clinical use, including diuretics, α-blockers, β-blockers, Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin Receptor blockers (ARB), and organic calcium channel blockers (CCBs). All these drugs are being currently used in the treatment of hypertension and various disease conditions of the heart either alone or in combination.[7]

Previous studies showed losartan prevents more cardiovascular morbidity and death than atenolol for a similar reduction in BP and is better tolerated. Losartan seems to confer benefits beyond reduction in BP.[3,5,8] Whereas, atenolol is a second-generation beta-1 (cardioselective) adrenergic antagonist, it blocks β1 receptors in heart thus decreasing the heart rate and workload. Despite being one of the widely prescribed β-blocker as losartan produces dizziness or light headedness at the beginning of the therapy, whereas atenolol is also known for its side effects like cold hands, feet, dizziness, diarrhea, etc.[9]

Additionally, dyslipidemia is more commonly found in untreated hypertensives than normotensives, and lipid levels increase as BP does. Though no specific pattern, dyslipidemia has been consistently reported among hypertensive individuals and shown that total cholesterol (TC), triglycerides (TG), and all fractions of lipoproteins tend to be more frequently abnormal.[10,11] This prospective study, an attempt has been made to compare the tolerability of losartan and atenolol as in hypertensive patients

## Methods

The study was conducted by the Department of Pharmacology in collaboration with the Department of Medicine on newly diagnosed patients of essential hypertension attending medicine outpatient department patients of Bidar institute of medical sciences, Bidar, for a period of 12 months from January 2019-December 2019. The study was conducted after the approval of the Institutional ethical committee (IEC).

### *Study Design*

It was a prospective, open-label, parallel group, and comparative study. Patients were screened in two steps, initial clinical examination by a physician followed by required biochemical examinations includes electrocardiogram (ECG), 2D ecocardiograph (ECHO), and lipid profile. History of comorbidities, allergies, past hospital admissions, reproductive history and addictions was obtained.

As many 100 patients were recruited for a period of 6 months and were called for follow-up visit at third and sixth month. The data collected was entered into a specially designed proforma (case recording form) for the study. Routine investigations were performed in hospital laboratory which included complete blood count, random blood glucose levels, liver function test (AST and ALT), renal function test (urea and creatinine) were also performed before and after institution of therapy according to the scheduled requirements.

The radial pulse was examined for the pulse rate and BP was recorded with a Mercury Sphygmomanometer in upright position. Adverse drug reactions (ADR) profile was assessed through a pretested questionnaire (Annexure 1) in both the groups. The questions were related to the frequency of hypertensive attacks, ADRs after taking the medicine and treatment taken for the ADRs.

Fifty patients of each were classified into losartan and atenolol group.

- Group A- 50 patients who were prescribed losartan tablet (50mg/day)
- Group B- 50 patients who were prescribed atenolol tablet (50mg/day)

*Inclusion Criteria*

1. Newly diagnosed with mild and moderate hypertensive patients.
2. Patients of either sex
3. Aged 40 to 60 years old
4. Patients who are willing to give informed consent.

*Exclusion Criteria*

1. Patients aged <18 years and >60 years.
2. In patients
3. History of severe hepatic, renal disease, severe cardiac diseases ,cancer patients
4. Pregnant and lactating mothers
5. History of major depressive disorder with psychotic symptoms
6. Patients on drugs with known drug interactions with the study drugs.

Patients were informed in detail about the study procedure and written informed consent was taken from all the subjects before including them in the study.

*Statistical Analysis*

All the data collected was entered into a preapproved, case recording form and tabulated using Microsoft Office Excel software. Data was analyzed using the IBM SPSS version 22.0 Armonk, NY, USA. Quantitative data are presented as means & standard deviation (mean ± SD) and qualitative data as frequency and 95% confidence interval (CI). Change of BP readings from baseline to end of study were compared using ANOVA and paired t test. Intergroup analysis was done using paired student's t-test. Significance was defined as $P < 0.05$.

**Results and Discussion**

Hypertension being a common health problem, is usually a progressive disorder, and one of the leading causes of death and disability worldwide. It is a major risk factor for cardiovascular diseases.[10,11] Lowering of elevated BP decreases morbidity from cardiovascular, cerebral and renal failure.[12] Essential hypertension is a condition where the cause for rise in blood pressure is not known.[13] The beneficial effects of antihypertensive agents on cardiovascular system can be counter balanced by the induction of metabolic disorders.

The modifications in various metabolic parameters like lipids, serum electrolytes, serum uric acid, and blood sugar level are responsible for different ADR of

**Table 1. Profile of Blood Pressure**

| Blood Pressure | | Group A (n=50) | Group B (n=50) | P value |
|---|---|---|---|---|
| Systolic | Baseline | 150.74±3.23 | 151.04±4.54 | 0.704 |
| | 3-months | 144.40±4.48 | 146.88±4.59 | 0.007 |
| | 6-months | 137.8±5.16 | 139.44±5.42 | 0.125 |
| Diastolic | Baseline | 94.02±4.99 | 94.88±3.57 | 0.324 |
| | 3-months | 89.36±4.59 | 90.64±4.05 | 0.143 |
| | 6-months | 84.86±12.86 | 88.0±4.69 | 0.108 |

antihypertensive drugs. It might also have potential to produce secondary morbidities after long term use. Several studies comparing antihypertensive agents have shown differences in risk reduction in cardiovascular diseases (CVD) with a similar blood pressure lowering effect, suggesting that specific pharmacological mechanisms may be involved.[11,12]

ARBs are increasingly used in the treatment of hypertension because of fewer side effects with blood pressure lowering abilities. The first ARB discovered was losartan. It is a competitive antagonist and an inverse agonist, about 10,000 times more selective for AT1 than AT2 receptors. It generates active metabolite which is more potent & non-competitively blocks the AT1 receptor with higher affinity. Blockade of AT1 receptors causes inhibition of vasoconstriction, sodium retention & reduces BP.[14,15]

In this present study, total of 100 patients were randomly allocated to receive losartan 50 mg (group A) or atenolol 50 mg (group B). Mean age of the patients was 52.72 years with a range from 42 years to 64 years. In this study, only 3% patients were elderly (>60 years). Males predominated females in both group A (66% vs. 34%) and group B (62% vs. 38%). There were 43 patients had a family history of hypertension. Out of these 43 patients, 25 patients in group A and 18 patients in group B had family history of hypertension. Mean BMI of the patients was 24.42 kg/m$^2$ with a range from 18.9 kg/m2 to 34.6 kg/m$^2$

The measurement of BP was routinely done. Systolic BP at 3-months was significantly lower in group A in comparison to group B, however, diastolic BP at 3-months was comparable between both groups. Both systolic and diastolic BP at 6-months was comparable between both groups.(Table 1)

Our study is one of the few studies to compare regression of ECG LVH between two active treatment arms. From ECG examination, mild LVH was found in either group (group A: 44%; group B: 46%). At 3-months, there were a significantly less number of patients with LVH on ECG examination in group A in comparison to group B (16% vs. 36%; P=0.022). At 6-months, 12% patients in group A and 18% in group B had mild LVH (P=0.400)

Losartan was significantly more effective in regressing LVH at 3- as well as 6-months in comparison to atenolol. Previous studies of LVH at 3- as well as 6-months in comparison to atenolol. Previous studies of regression of ECG LVH during antihypertensive therapy

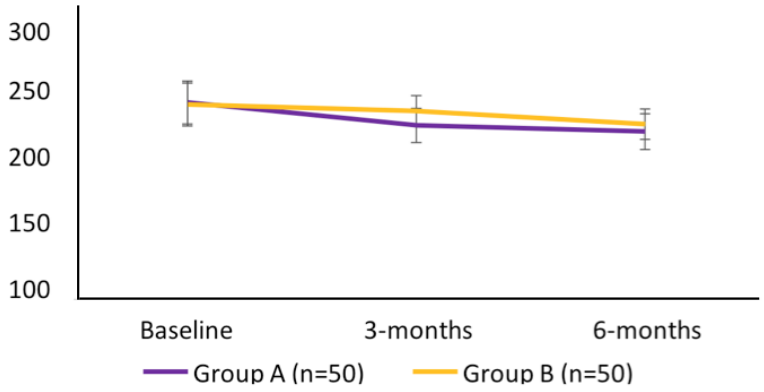


**Figure 1. Comparison of Total Cholesterol**

have been limited by failure to directly compare two active treatment arms.[16,17] In "The Losartan Intervention for Endpoint reduction in Hypertension (LIFE) Study", Okin et al[18] reported that losartan-based antihypertensive therapy resulted in greater regression of ECG LVH by Cornell voltage-duration product and Sokolow-Lyon voltage criteria than did atenolol-based therapy. These findings support the value of angiotensin receptor blockade with losartan for reversing ECG LVH.

At all-time points through 6-months of study treatment, losartan therapy was associated with significantly lower prevalence of ECG LVH from study baseline. The greater reduction in ECG LVH with losartan in the setting of similar reductions in BP with both therapies suggests a potential antihypertrophic effect of losartan, possibly mediated by direct blockade of myocardial effects of angiotensin II.[19] In this present study, from 2D ECHO, LVH was found in either group (group A: 36%; group B: 32%; P=0.672). There were a significantly less number of patients with LVH on ECG examination in group A in comparison to group B at 3-months (12% vs. 28%; P=0.045) and 6-months (10% vs. 26%; P=0.037). Previous studies demonstrating that increased regression of echocardiographic LVH with ACE inhibition was in part independent of BP reductions[20] further suggest a possible nonhemodynamic contribution of the renin-angiotensin system to hypertrophy.

It was observed in our study that ADR was commonly found in patients using atenolol than losartan. Most common ADR in atenolol group was headache (24%), nausea and vomiting (18%), dizziness, palpitation and tachycardia (14%), GI disturbances anand hypotension (12%), blurring of vision(20%), pedal edema(8%), urinary problems (6%) and flushing( 4%). Whereas the most common adverse effects seen in losartan group was dizziness ( 24%), followed by gastrointestinal disturbances ( 20%), headache (14%), nausea (12%), and hypotension (6%). All the adverse effects noted in our study were mild to moderate and no patient withdrew because of adverse effects.

In lipid profile, both losartan as well as atenolol significantly reduced TC (Figure 1), TG (Table 2), and LDL (Table 3), while increased HDL levels at 3- as well as 6-months, a more significant effect was observed in losartan group (Table 4). Olsen et al reported that losartan blunted the decrease in HDL cholesterol during antihypertensive treatment in the LIFE study. Higher in-treatment HDL cholesterol may partly explain the better outcome of losartan-based treatment.[21]

**Table 2. Comparison of Triglycerides**

| | Group A (n=50) | Group B (n=50) | P value |
|---|---|---|---|
| Baseline | 178.48±49.69 | 181.90±30.29 | 0.679 |
| 3-months | 150.96±46.95 | 173.02±26.87 | 0.005 |
| 6-months | 134.08±42.66 | 159.48±26.76 | 0.001 |

**Table 3. Comparison of LDL Levels**

| | Group A (n=50) | Group B (n=50) | P value |
|---|---|---|---|
| Baseline | 167.98±44.15 | 173.98±56.70 | 0.556 |
| 3-months | 135.02±38.92 | 159.42±45.70 | 0.005 |
| 6-months | 114.70±33.46 | 133.16±43.64 | 0.019 |

**Table 4. Comparison of HDL Levels**

| | Group A (n=50) | Group B (n=50) | P value |
|---|---|---|---|
| Baseline | 33.38±3.24 | 32.37±2.28 | 0.074 |
| 3-months | 44.55±3.47 | 39.81±2.76 | <0.01 |
| 6-months | 45.65±2.63 | 41.09±1.85 | ,0/01 |

The observation that losartan-based compared with atenolol-based treatment was associated with higher HDL-C and lower non-HDL-C throughout the study confirms previous reports[22,23] that beta-adrenergic receptor blockers have negative effects on lipid metabolism, whereas angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have neutral or positive effects. These treatment differences in HDL-C and non-HDL-C were independent of baseline characteristics and weight changes. Limitation of the study is large sample size is required to validate the findings.

## Conclusion

Our study observed that both losartan and atenolol are equally effective in long- term reduction of blood pressure. Both atenolol and losartan were tolerated well by the patients despite adverse reactions occurring due to these drugs Additionally, losartan also significantly improved lipid profile in terms of decreasing total cholesterol, triglycerides, and LDL, and increasing HDL.

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## Conflict of Interest

Nil

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**Table 5. Comparative Assessment of Adverse Drug Reactions**

| ADRs | Drugs | |
|---|---|---|
| | Group A (n=50) | Group B (n=50) |
| Pedal Edema | - | 4 |
| Headache | 7 | 12 |
| GI Disturbances | 10 | 6 |
| Dizzines | 10 | 6 |
| Hypotension | 2 | 6 |
| Palpitation/Tachycardia | - | 7 |
| Blurring Vision | - | 5 |
| Flushing | - | 2 |
| Urinary Problem | - | 3 |
| Nausea/Vomiting | 6 | 9 |
| Others | 3 | 7 |
| Total | 40 | 68 |

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