

# Uric Acid Lowering Effect of Losartan in Patients with Stage 1 Hypertension and Asymptomatic Hyperuricemia

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**Abstract-** Hyperuricemia is a recognized risk factor for cardiovascular diseases, particularly prevalent in individuals with hypertension. Addressing hyperuricemia holds the potential to mitigate the onset of hypertension. This investigation focused on exploring the uric acid-reducing capabilities of losartan in patients exhibiting stage 1 hypertension (as per JNC VIII) accompanied by asymptomatic hyperuricemia. Conducted as a community-based before-and-after interventional study, this research involved 27 male participants with stage 1 hypertension and asymptomatic hyperuricemia. The intervention comprised a treatment regimen of losartan, initially at 25 mg once daily for 4 weeks, followed by an escalation to 50 mg once daily for the subsequent 4 weeks, totaling 8 weeks of continuous therapy. Serum uric acid levels were assessed at baseline, after 4 weeks of 25 mg losartan, and following an additional 4 weeks of 50 mg losartan therapy. Comparative analysis with baseline data revealed a significant reduction in blood pressure with both losartan doses, although serum uric acid level did not show a significant decrease. Notably, the dose-dependent effect on serum uric acid level was evident, with a 1.80 % reduction after 4 weeks of 25 mg losartan and a 6.52 % reduction after 4 weeks of 50 mg losartan. In summary, while losartan demonstrated a dose-dependent effect in lowering uric acid levels, achieving normal range values may necessitate larger doses and extended therapy duration.

**Index Terms-** Hypertension, Hyperuricemia, Losartan, Serum Uric Acid (SUA)

## I. INTRODUCTION

Hyperuricemia emerges as a potential precursor to insulin resistance, hypertension, dyslipidemia, and cardiovascular diseases, with a higher prevalence observed in developed nations, although an escalating trend is discernible in several developing countries (1–3). The association between hypertension and hyperuricemia has been substantiated, particularly in individuals with elevated BMI and those aged over 60 years (4). Hyperuricemia, if left unmanaged, can lead to gouty arthritis, hyperuricemic nephropathy, and uric acid nephrolithiasis, with the majority of affected individuals remaining asymptomatic (5).

A significant higher association was observed with various comorbidities, including hypertension, chronic kidney disease, obesity, diabetes, nephrolithiasis, myocardial infarction, heart failure, and stroke, in individuals with hyperuricemia, reaching markedly elevated prevalence rates in those with serum uric acid  $\geq 10$  mg/dL (6). Experimental and human data robustly establish uric acid's pivotal role in hypertension, revealing a consistent association between progressively elevated serum uric acid levels and a proportional increase in the relative risk of new-onset hypertension (7). Normotensive individuals with serum uric acid levels exceeding 7 mg/dL face an 80% elevated risk of developing hypertension (8).

Although conventional therapies for hyperuricemia, such as allopurinol, benzbromarone, febuxostat, and probenecid are effective in lowering uric acid levels, research has explored alternative drugs not primarily indicated for hyperuricemia, revealing the antihyperuricemic effects of losartan, an angiotensin II receptor blocker typically employed as an antihypertensive agent (9–13).

While angiotensin receptor blockers and calcium channel blockers are established first-line treatments for hypertension(14), their impact on serum uric acid levels varies. Diuretics and  $\beta$ -blockers are associated with elevated serum uric acid levels, whereas calcium-channel blockers and losartan exhibit a uric acid-lowering effect, with consistent reports linking them to a decreased risk of gout incidence (15). Investigations into the antihyperuricemic effects of losartan at varying dosages demonstrated promising outcomes. A study involving 30 patients receiving losartan 50 mg daily for 12 weeks reported a substantial reduction in serum uric acid levels from

8.09 ± 0.62 mg/dL at baseline to 6.24 ± 0.33 mg/dL at 12 weeks (p<0.0001)(9). Similarly, another study administering losartan 20-50 mg daily for 6 months witnessed a decline in serum uric acid levels from 4.02 ± 0.72 mg/dL to 3.61 ± 0.45 mg/dL (p<0.0001) after 6 months of monotherapy(11).

Previous investigations have established the uric acid-lowering effect of losartan, predominantly at a 50 mg daily dosage, prompting the present study to explore dose-dependent effects. This study aims to evaluate the antihyperuricemic efficacy of losartan in patients with stage 1 hypertension and asymptomatic hyperuricemia over an 8-week period. The choice of losartan is pertinent due to its dual role as an antihypertensive and potential antihyperuricemic agent, with a dosage range of 25-100 mg. If successful, this study may offer insights into the optimal dosage required for effectively managing asymptomatic hyperuricemia and preventing associated complications, thereby contributing valuable data to the evolving landscape of hyperuricemia and hypertension research.

## II. MATERIALS AND METHODS

The aim of the study was to investigate the uric acid-lowering effect of losartan in patients diagnosed with stage 1 hypertension and presenting asymptomatic hyperuricemia. The study design is community-based before-and-after interventional study. The research was conducted from March 2020 to December 2021 in GP clinics in Mingalardon and Shwe-Pyi-Thar townships, as well as the community in Bahan and Sanchaung townships, Yangon, Myanmar. Male patients with stage 1 hypertension (140/90-159/99 mmHg) and asymptomatic hyperuricemia between 18 and 75 years of age with BMI ≤ 35 kg/m<sup>2</sup> were included in the present study. Patients who were already taking anti-hypertensive drugs or drugs affecting serum uric acid level, had history of significant liver or renal diseases, already have symptoms of gouty arthritis or were alcoholics were excluded.

Adult patients with stage 1 hypertension were invited, and after explaining the study, those providing written informed consent were screened for asymptomatic hyperuricemia using a uric acid meter (manufactured by Guilin Royalize Medical Instrument Co., Ltd). History taking and basic clinical examination were performed to those meeting the inclusion criteria. Patient's demographic data including age, body weight (kg), height (cm); clinical findings including BP, HR, data of basic clinical examination were noted down in pro-forma. Baseline BP and fasting serum uric acid (SUA) level was noted. Baseline fasting SUA was determined after 10 hours of fasting using UV-VIS Spectrophotometer (Model: PD-303UV) at RIGHT laboratory, Yangon, Myanmar. Then, the patients were treated with 25 mg losartan daily for 4 weeks, followed by an escalation to 50 mg daily for an additional 4 weeks. Blood pressure and fasting SUA level were rechecked after 4 weeks of 25 mg losartan, and after 4 weeks of 50 mg losartan (at the end of 8<sup>th</sup> week of losartan therapy).

BP and SUA among baseline, after 4 weeks of 25 mg losartan, and after 4 weeks of 50 mg losartan were analyzed and compared by using statistical package of statistical product and service solution (SPSS) version 16. The p value (< 0.05) was considered as statistically significant.

This study was approved by the Academic Board of Studies for Master of Medical Science (Pharmacology) of Defence Services Medical Academy, Yangon, Myanmar.

## III. RESULTS

The uric acid lowering effect of losartan was studied in 27 newly diagnosed stage 1 hypertensive patients with asymptomatic hyperuricemia. The age range of the study population was 25 years to 72 years male patients with the range of BMI from 20.1 to 33.4. The mean age of patients was 50 ± 13.25 years and mean BMI of patients was 26.07 ± 3.01 kg/m<sup>2</sup> (Table 1).

**Table 1. Mean age and BMI of the studied patients (n=27)**

<b>Parameters</b>	<b>mean ± SD</b>
<b>Age (year)</b>	50 ± 13.25
<b>BMI (kg/m<sup>2</sup>)</b>	26.07 ± 3.74

At baseline, the mean systolic blood pressure (SBP) was  $155.18 \pm 4.37$  mmHg. After 4 weeks of losartan 25 mg treatment, the mean SBP decreased to  $153.51 \pm 5.99$  mmHg ( $p=0.187$ ) and after 4 weeks of losartan 50 mg treatment, decreased to  $143.03 \pm 6.30$  mmHg ( $p=0.000$ ). The % changes of SBP was 1.02 and 6.72. Before treatment with losartan, the mean diastolic blood pressure (DBP) was  $92.88 \pm 2.04$  mmHg. After 4 weeks of losartan 25 mg therapy, the mean DBP significantly decreased to  $89.37 \pm 2.66$  mmHg ( $p=0.000$ ) and after 4 weeks of losartan 50 mg therapy, decreased to  $84.88 \pm 4.13$  mmHg ( $p=0.000$ ). Percent changes of DBP was 3.77 and 4.89%. These data are shown in (Table 2) and (Table 3).

**Table 2. Comparison of mean blood pressures at baseline and after 4 weeks of losartan 25 mg in studied patients (n = 27)**

Parameters	Week 0	Week 4	% Change	<i>p</i> value
	(mean ± SD)	(mean ± SD)		
	(mmHg)	(mmHg)		
<b>SBP</b>	$155.18 \pm 4.37$	$153.51 \pm 5.99$	1.02	0.187
<b>DBP</b>	$92.88 \pm 2.04$	$89.37 \pm 2.66$	3.77	0.000

**Table 3. Comparison of mean blood pressures after 4 weeks of losartan 25 mg and after 4 weeks of losartan 50 mg in studied patients (n = 27)**

Parameters	Week 4	Week 8	% Change	<i>p</i> value
	(mean ± SD)	(mean ± SD)		
	(mmHg)	(mmHg)		
<b>SBP</b>	$153.51 \pm 5.99$	$143.03 \pm 6.30$	6.72	0.000
<b>DBP</b>	$89.37 \pm 2.66$	$84.88 \pm 4.13$	4.89	0.000

In studied patients, baseline mean SUA level was  $484.39 \pm 67.85$   $\mu\text{mol/L}$ . After 4 weeks treatment with losartan 25 mg, the mean SUA level decreased to  $475.30 \pm 66.47$   $\mu\text{mol/L}$  and after 4 weeks treatment with losartan 50 mg, it decreased to  $443.95 \pm 69.66$   $\mu\text{mol/L}$ . These data are shown in (Table 4). Therefore, mean serum uric acid levels reached to upper normal limit in patients after treatment with losartan 50 mg for 4 weeks (Upper normal limit of male serum uric acid level is 420  $\mu\text{mol/L}$ ).

**Table 4. Comparison of serum uric acid level at baseline, after 4 weeks of losartan 25 mg therapy and after 4 weeks of losartan 50 mg therapy in studied patients (n=27)**

Parameter	Baseline	After 4 weeks of losartan 25 mg	After 4 weeks of losartan 50 mg	<i>p</i> value
	(mean ± SD)	(mean ± SD)	(mean ± SD)	
<b>Serum uric acid (<math>\mu\text{mol/L}</math>)</b>	$484.39 \pm 67.85$	$475.30 \pm 66.47$	$443.95 \pm 69.66$	0.079

Percent change of mean SUA levels was 1.8% reduced after 4 weeks of 25 mg losartan and 6.52% reduced after 4 weeks of 50 mg losartan therapy (Table 5).

**Table 5. Comparison of uric acid % change after 4 weeks of losartan 25 mg and after 4 weeks of losartan 50 mg therapy in studied patients (n=27)**

Parameter	After 4 weeks of 25 mg losartan	After 4 weeks of 50 mg losartan	Difference	p value
<b>Serum uric acid % change</b>	1.80	6.52	4.72	0.004

#### IV. DISCUSSION

Hyperuricemia, characterized by elevated SUA levels, has emerged as a significant risk factor for cardiovascular disease and hypertension. Given the coexistence of these conditions in a substantial number of patients, antihypertensive agents are commonly prescribed to individuals with hyperuricemia. However, the influence of various antihypertensive drugs on SUA levels varies based on their distinct pharmacological actions. This study aimed to explore the dual therapeutic benefits of losartan, an angiotensin receptor blocker, by investigating its antihyperuricemic and anti-hypertensive effects in newly diagnosed stage 1 hypertensive patients with asymptomatic hyperuricemia.

The study exclusively enrolled male participants. The intervention involved the administration of losartan at 25 mg once daily for the initial 4 weeks, followed by an increased dosage of 50 mg for the subsequent 4 weeks. Despite facing challenges in recruitment due to Covid-19 pandemic, the study achieved a cohort of 27 participants, all of whom demonstrated excellent compliance by completing the 8-week interventional therapy. Following the 25 mg regimen, a modest decrease in mean SBP and DBP was observed. However, the 50 mg regimen demonstrated a more substantial reduction, with both SBP and DBP levels significantly decreased (p=0.05).

Several studies have investigated the antihypertensive and antihyperuricemic effects of losartan. In a study by Rayner et al. (2006), 27 hypertensive patients received losartan at doses ranging from 50 to 100 mg for 24 weeks. Significant decreases were observed in SBP, DBP, and serum uric acid (SUA) levels over the study duration(16). Another study by Dang et al. (2006) showed that losartan at 50 mg once daily produced a substantial decrease in SUA levels over 8 weeks. The study reported a median decrease from 422 mmol/L at baseline to 359 mmol/L after 8 weeks, coupled with notable improvements in blood pressure(12). Similarly, Sharma et al. (2018) investigated thirty patients who received losartan at 50 mg once daily for 12 weeks. The study reported significant decreases in SUA levels, SBP, and DBP over the 12-week period(9). Additionally, Khan et al. (2021) explored a decrease in serum uric acid levels from 8.21 mg/dl at baseline to 6.19 mg/dL after 12 weeks of losartan 50 mg once daily therapy (p< 0.001)(13).

In the present study, the impact on SUA levels was more pronounced with the 50 mg dose of losartan. After 4 weeks of losartan 25 mg therapy, there was a nominal decrease in mean SUA levels. However, losartan 50 mg demonstrated a substantial reduction (p=0.004). Notably, the dose-related percentage change in SUA levels after 4 weeks of losartan 50 mg was 6.52%, indicating a clear relationship between dosage and the antihyperuricemic effect. Despite the positive findings, it is crucial to note that the SUA level did not reach normal ranges within the 8-week duration. This suggests that higher doses and prolonged durations may be necessary to achieve optimal efficacy in reducing SUA level.

#### V. CONCLUSION

This study significantly contributes valuable insights into the dual therapeutic benefits of losartan in newly diagnosed stage 1 hypertensive male patients with asymptomatic hyperuricemia. The findings underscore the dose-dependent anti-hyperuricemic effect of losartan, suggesting that higher doses and extended durations may be necessary to achieve normal SUA level. This study adds to the growing body of evidence supporting the multifaceted benefits of losartan in managing both hypertension and hyperuricemia, emphasizing its potential as a comprehensive therapeutic agent for individuals with these coexisting conditions. Further research with larger sample sizes and extended follow-up periods is warranted to elucidate the full spectrum of losartan's therapeutic effects in this context.

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