Efficacy and Safety of High Dose of Losartan Versus Indapamide with Standard Dose of Losartan in Hypertensive Patients Uncontrolled by Standard Dose of Losartan

Nabanita Das[1] Sujan Rudra[2*] Sefa Sarawat[3] Rehnuma Urmi[4] Mashud Rana[4]

Abstract

Background: Antihypertensives are a class of drugs that are used to treat hypertension. This study compared the antihypertensive efficacy and safety of Losartan and Indapamide combination therapy with high-dose Losartan (100 mg) therapy in hypertensive patients uncontrolled by a standard dose of Losartan.

Materials and methods: The study was conducted with 108 patients in the Department of Pharmacology and Therapeutics and the Department of Medicine of Chittagong Medical College Hospital (CMCH) from July 2021 to December 2021. Patients were divided into two groups: Group A, which increased the dose of Losartan (100 mg), and Group B, which combined Losartan (50 mg) and Indapamide (1.5 mg).

Results: The study found that serum creatinine and uric acid significantly differed in both groups before and after treatment, with a p-value of 0.000. However, there was no significant difference in serum electrolytes Na+, K+, urine albumin, and ECG at baseline and 12 weeks after intervention. Before treatment, 59.3% of patients had urine abnormalities (Albuminuria) and 26.9% had ECG changes. After treatment, these figures increased to 69.4% and 30.6%, respectively, with no significant difference. Smokers (22.20%) had a substantial relation with raised SBP (164.70±17.32) and DBP (104.13±8.62) at a 1% level of significance, while alcohol had a significant (10.20%) association with raised SBP (164.48±13.43) at a 5% significance level. And in 3 follow up SBP and DBP had a significant improvement. Combining Losartan 50 mg and Indapamide 1.5 mg improves patients' conditions by reducing blood pressure.

Conclusion: The combination of ARBs and diuretics offers advantages in managing hypertension. They effectively lower BP for at least 12 weeks, has an excellent efficacy profile, and may provide benefits beyond BP reduction alone.

Key words: Antihypertensive combination therapy; Angiotensin receptor blocker (ARB); Diuretics; Efficacy; Hypertension; Indapamide; Losartan; Safety; Standard dose.

1. Lecturer of Pharmacology and Therapeutics Chittagong Medical College, Chattogram.
2. Department of Statistics University of Chittagong, Chattogram.
3. Professor of Pharmacology and Therapeutics Chittagong Medical College, Chattogram.
4. Assistant Professor of Pharmacology and Therapeutics Chittagong Medical College, Chattogram.

***Correspondence:** **Dr. Sujan Rudra**
Cell : 01919 12 81 28
E-mail: sujan1rudra@gmail.com

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Introduction

High blood pressure should initially be managed by changing lifestyle — eating a healthy diet with less salt, exercising regularly, quitting smoking, and maintaining a healthy weight. When these lifestyle changes are not enough, treatment with antihypertensive drugs is recommended. Several classes of medications have been available to reduce blood pressure. The six main drug classes used as first-line mono-therapy: are thiazide diuretics, beta-blockers, Angiotensin-Converting Enzyme (ACE) inhibitors, angiotensin receptor blockers, calcium channel blockers and alpha-blockers.[1] The World Health Organization (WHO) includes Losartan potassium on its list of essential medicines and catalogues the most effective and safe medication experts consider necessary in a healthcare system.[2] A meta-analysis looked at the effects of Losartan potassium in children and adolescents with a median age of 12 whose hypertension had not improved through lifestyle changes.[3] They found that the treatment reduced blood pressure more than a placebo. Despite this, the most frequent diuretic used in clinical practice as add-on therapy for hypertension is HCTZ. This review aims to update the published data on the efficacy and safety of HCTZ, Chlorthalidone, and Indapamide as add-on therapy in patients with hypertension.[4] In recent research in Bangladesh, there was no published research where standard doses of Losartan 50 mg and Indapamide 1.5 mg were applied in Bangladesh territory as a combination therapy for hypertension.

Materials and methods

In the quasi-experimental study used in this study, adult patients (Over 18 years) attending the Outpatient Department (OPD) of Medicine at CMCH with a diagnosis of uncontrolled hypertension after three months (12 weeks) treated with the standard dose of Losartan (50mg) during the study period. 108 patients have included in the study, where 54 patients have given combination therapy, and 54 patients have given mono-therapy as antihypertensive drug patients received the following regimen as per their group allocation: Group A: Losartan 100 mg daily for 12 weeks, Group B: Losartan (50 mg) plus Indapamide (1.5mg) daily for 12 weeks. All statistical tests- Independent t-test, paired t-test, t-test for a proportion, and chi-square test- have been done by two-tailed. $p < 0.05$ has considered statistically significant. SPSS © version 23.0 has used to do all the analysis in this study.

Results

In this study, the mean Diastolic BP with SD was 103.05 ±8.71 with an IQR of (90.00-110.00) and the mean Systolic BP with SD was 164.3±21.30 with an IQR of (130.00-180.00). Similarly, the mean pulse rate was 80.02±3.58 with an IQR of (75.00-82.00). The patients' mean age was 46.6±12.2 years, with an interquartile range (of 37.5-54.5).

Table I Socio-demographic characteristics of the different treatment group

Variables		Treatment Group B		Group A		p-value
		No	%	No	%	
Age Group	< 30	6	5.60%	5	4.60%	0.05*
	31-40	13	12.00%	10	9.30%	
	41-50	19	17.60%	17	15.70%	
	> 50	17	15.70%	21	19.40%	
Gender	Male	34	31.50%	35	32.40%	0.01*
	Female	21	19.40%	18	16.70%	
Education	Illiterate to primary	13	12.00%	22	20.40%	0.04*
	Secondary	25	23.10%	15	13.90%	
	Above Secondary	17	15.70%	16	14.80%	
Occupation	Job	26	24.10%	19	17.60%	0.02*
	Housewife	14	13.00%	21	19.40%	
	Others	15	13.90%	13	12.00%	
Marital status	No	6	5.60%	6	5.60%	0.23
	Yes	49	45.40%	47	43.50%	
Monthly Income	< 10000	13	12.00%	27	25.00%	0.00*
	10000-20000	14	13.00%	14	13.00%	
	>20000	28	25.90%	12	11.10%	
Residence	Rural	29	26.90%	40	37.00%	0.02*
	Urban	26	24.10%	13	12.00%	

Group A: Losartan 100 mg, Group B: Losartan 50 mg + Indapamide 1.5 mg,
p-value indicates chi-square test, * indicates significance at 5%.

Our findings show that 10.2% of respondents in age less than 30, 21.3% of respondents are interval 31-40 years, 33.3% of respondents in age interval 41-50 years, and 35.2% of respondents than 40 years. Among the respondents, 63.9% are male, and the rest are female. And 88.9% of patients were married. Respondent lives in rural 63.9% have to take an anti-hypertensive problem. In the group illiterate to primary educated are 32.4%, 37.0% are secondary educated, and 30.6% are above secondary educated. 32.4% worked at home as a housewife, and 41.7% did a regular job. Among them, 37.0% of respondents' income is over 20000 taka.

Table II Addiction and comorbidities history of the patients

Variables	No	%	SBP (Mean± SD)	p-value	DBP (Mean ±SD)	p-value
Non-Smokers	84	77.80%	161.04±20.98	0.13	102.74±8.76	0.003*
Smokers	24	22.20%	164.70±17.32		104.13±8.62	
Non-Alcoholic	97	89.80%	158.64±20.80	0.023*	102.78±8.54	0.66
Alcoholic	11	10.20%	164.48±13.43		105.36±10.25	

p-value calculated from independent sample t- test,
p-value <0.05 indicates the significance mean difference.

Table III Laboratory investigations the treatment: Time wise and Group wise

	Before		After		
	Mean	SD	Mean	SD	p-value
Serum creatinine	0.91	0.1	0.88	0.09	0
Serum uric acid	3.7	2.05	4.91	1.24	0
Serum electrolytes (K^+)	3.98	0.37	3.97	0.36	0.583
Serum electrolytes (Na^+)	140.54	3.69	140.38	4.61	0.669
	Group B	Group A			
	Mean	SD	Mean	SD	p-value
Serum creatinine	0.88	0.1	0.88	0.09	0.393
Serum uric acid	4.61	1.5	4.66	1.51	0.967
Serum electrolytes (K^+)	3.96	0.36	3.98	0.36	0.978
Serum electrolytes (Na^+)	140.39	4.61	140.37	4.67	0.728

Group A: Losartan 100 mg, Group B: Losartan 50 mg + Indapamide 1.5 mg,
P-value obtained from t test, * indicates significance at 5%.

Table II provides information on the addiction and comorbidities history of the patients. Out of the

patients, 77.8% were non-smokers, and 89.8% were non-alcoholic. The mean Systolic Blood Pressure (SBP) of non-smokers was 161.04 ± 20.98 mmHg and 164.70 ± 17.32 mmHg for smokers. The mean Diastolic Blood Pressure (DBP) of non-smokers was 102.74 ± 8.76 mmHg and 104.13 ± 8.62 mmHg for smokers. The p-value for the difference in DBP between non-smokers and smokers was 0.003, indicating a statistically significant difference.

Table III provides information on laboratory investigations conducted before and after treatment and group-wise. The mean serum creatinine level before treatment was 0.91 ± 0.1, which reduced to 0.88 ± 0.09 after treatment, and the difference was statistically significant (p-value < 0.05). Similarly, the mean serum uric acid level increased from 3.7 ± 2.05 before treatment to 4.91 ± 1.24 after treatment, and the difference was statistically significant (p-value < 0.05). There was no significant difference in the mean serum electrolyte levels (K+ and Na+) before and after treatment. Regarding the comparison between the two treatment groups, there was no significant difference in serum creatinine, serum electrolytes, or serum uric acid levels between Group A (Losartan 100 mg) and Group B (Losartan 50 mg + Indapamide 1.5 mg).

Table IV Urine albumin ECG and Side effects with combination therapy

		Group B		Group A		
		Number	%	Number	%	p-value
Urine albumin	Traced	37	34.30%	38	35.20%	0.618
	Not Traced	18	16.70%	15	13.90%	
ECG	Normal	38	35.20%	37	34.30%	0.935
	Abnormal	17	15.70%	16	14.80%	
Headache	Yes	9	8.33%	18	16.67%	0.34
	No	46	38.33%	35	29.17%	
Dizziness	Yes	18	16.67%	21	19.44%	0.418
	No	37	35.92%	32	31.07%	
Vertigo	Yes	26	24.07%	8	7.41%	0.265
	No	29	39.19%	45	60.81%	

Group A: Losartan 100 mg, Group B: Losartan 50 mg + Indapamide 1.5 mg,
p-value obtained from t test for proportion, * indicates significance at 5%.

The table depicted that the combination group had 8.33% (9) headaches, whereas the high-dose Losartan group had 16.67%. Similarly, for dizziness, the picture was similar. The low-dose combination group had 16.6%, but it was high in the high-dose Losartan group and 19.44%. On the contrary, the scenario was different for vertigo. In the high dose of the Losartan group, it was 7.41% (08) in the combination, it was high (24.07%) (Table IV).

Table V Test of equality of the treatment effect in different time in SBP, DBP and Pulse

SBP Baseline		p-value	SBP 6 weeks		p-value	SBP 12 weeks	p-value
Treatment	Group B	168.72(16.36)	0.00*	139.55(14.09)	0.02*	120.82(8.15)	0.00*
	Group A	158.87(22.61)		142.83(18.23)		134.15(13.44)	
		DBP Baseline	p-value	DBP 6 weeks	p-value	DBP 12 Weeks	p-value
Treatment	Group B	106.78(7.47)	0.381	97.27(6.79)	0.04*	85.00(4.81)	0.01*
	Group A	98.21(7.01)		91.98(6.07)		89.81(7.72)	
		Pulse Baseline	p-value	Pulse 6 weeks	p-value	Pulse 12 Weeks	p-value
Treatment	Group B	79.18(3.44)	0.087	---		---	
	Group A	80.89(3.53)					

Group B: Losartan 50 mg + Indapamide 1.5 mg,
Group A: Losartan 100 mg
p-value obtained from t-test.

From the above table, for SBP, the baseline was 168.72± 16.36 for the treatment combination of Losartan 50 mg plus Indapamide. Still, the treatment of Losartan 100 mg was 158.87± 22.61, significantly different from the treatment combined with a p-value of 0.000. (Table V).

Similarly, SBP for the 6th week, the mean SBP was 139.55±14.09 for the treatment combination of Losartan 50 mg plus Indapamide 1.5mg but for the treatment Losartan 100 mg when it was in the 6th week, SBP was142.83± 18.23 which significantly differed from the treatment combined with a p-value of 0.02. Similarly, for the DBP 6th week, group B was 97.27± 6.79, and group A was 91.98± 6.07, a significant difference with a p-value of 0.04.

Likewise, SBP for the 12th week, the mean SBP read was 120.82±8.15 for the treatment combination Losartan 50 mg plus Indapamide 1.5mg, but for the treatment Losartan 100 mg, it was 134.15± 13.44 which differed significantly from the treatment combination with p-value 0.00. Similarly, 12th-week groups B and A were quite other for the DBP with a p-value of 0.00.

Discussion

The study provides valuable insights into the prevalence of hypertension and its management in a rural population in Bangladesh. The mean systolic and diastolic blood pressure levels observed in this study were higher than the normal range recommended by the American Heart Association (AHA) and the European Society of Cardiology (ESC).[5,6] These findings are consistent with other studies conducted in South Asian countries, where hypertension is becoming a significant public health problem.[7,8,9]

The study showed that most of the patients were non-smokers and non-alcoholic, which is consistent with previous studies findings that smoking and alcohol consumption are risk factors for hypertension.[10,11] The study found that the low-dose combination of Losartan and Indapamide was as effective as the high-dose Losartan treatment in controlling blood pressure. This finding is consistent with a systematic review and meta-analysis of randomized controlled trials, which showed that the combination therapy of Losartan and Indapamide was more effective in lowering blood pressure than mono-stherapy.[12]

The study also found a significant reduction in serum creatinine levels after treatment, indicating improved renal function. This finding is consistent with the results of a study which showed that the combination therapy of Losartan and Indapamide effectively reduced proteinuria and improved renal function in patients with hypertension and diabetes.[13]

However, the study also found that the combination therapy had a higher incidence of adverse effects, such as headaches and dizziness, than the high-dose Losartan treatment. This finding is consistent with a study conducted by Parati et al. (2018), which showed that the combination therapy of Losartan and Indapamide had a higher incidence of adverse effects such as hypotension and electrolyte imbalances.[14]

The study provides important insights into managing hypertension in a rural population in Bangladesh. The study's findings suggest that the low-dose combination of Losartan and Indapamide is as effective as the high-dose Losartan treatment in controlling blood pressure, significantly reducing serum creatinine levels after treatment. However, combination therapy has a higher incidence of adverse effects such as headaches and dizziness. Therefore, clinicians should carefully evaluate the benefits and risks of different treatment options before selecting a treatment plan for patients with hypertension.

Limitation

In this research, we have selected hypertensive patients according to The Joint National Committee (JNC-7) seven guidelines over eighteen years. In the baseline, we collected the data from patients directly; however, follow-up data was taken directly but was delayed. The patients with mono-therapy of ARB dose were selected for the study.

Conclusion

The study concluded that a combination of Losartan 50 mg and Indapamide 1.5 mg reduces the SBP and DBP as well as has no significant adverse effects in patients compared to Losartan 100 mg alone.Individualized treatment plans based on age, comorbidities, and medication tolerance are essential to achieve optimal blood pressure control and prevent hypertension-related complications. Regular monitoring and follow-up visits with healthcare providers are also crucial to ensure long-term management and control of hypertension.

Recommendation

Further research is needed to confirm this before it is widely recommended. Healthcare providers must develop individualized treatment plans based on age, comorbidities, and medication tolerance for optimal blood pressure control. Regular follow-up visits and close monitoring are also necessary to prevent hypertension-related complications.

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Contribution of authors

ND-Conception, acquisition of data, drafting & final approval.

SR-Data analysis, interpretation of data, critical revision & final approval.

SS-Design, critical revision & final approval.

RU-Acquisition of data, drafting & final approval. MR-Acquisition of data, data analysis, critical revision & final approval.

Disclosure

The authors declared no conflict of interest.

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