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RESEARCH ARTICLE

Comparative evaluation of antihypertensive effects of Ramipril vs. Losartan in patients with uncomplicated stage-1 hypertension

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ABSTRACT

Background and Objectives: Hypertension is responsible for high morbidity and mortality in cardiovascular diseases. As Ramipril and Losartan are important ones due to extensive use, fewer side effects, low cost & availability in market, study was aimed to evaluate antihypertensive effects, tolerability & compliances of Ramipril & Losartan in patients with uncomplicated stage-1 hypertension in suburban & rural population. **Methods:** A randomized, single blind, parallel & cross over study was conducted in Medicine OPD of a tertiary care hospital for period of 12 months. Patients of both sexes, aged 25-60 years, with uncomplicated stage-1 hypertension were included. Patients with hypertension were checked for systolic blood pressure (SBP) / diastolic blood pressure (DBP) in sitting posture. Patients were randomly selected into 2 groups: group-A received tab. Ramipril (5 mg/day) & group-B received tab. Losartan (50 mg/day) at start of treatment, followed by wash-out period & then Losartan was given to group-A & ramipril to group-B. Paired t test applied between groups. **Results:** Our study revealed that both drugs reduced SBP & DBP gradually from baseline BP but Ramipril reduced more effectively & significantly ($p<0.001$) SBP & DBP than Losartan. **Conclusion:** Ramipril had better efficacy than Losartan in reduction of BP in stage-1 hypertensive patients with no complications, though it is slightly costlier.

Key words: Stage-1 hypertension, Ramipril, Losartan, SBP, DBP

INTRODUCTION:

An epidemiological shift in prevalence of hypertension (HTN) in developing countries including India as compared to developed countries has been observed.[1] Prevalence of HTN is increased by 30 times among urban population over a period of 55 years & about 10 times among rural population over a period of 36 years. Cardiovascular disease (CVD) is responsible for one third of global deaths & it is a leading & increasing contributor to global disease burden.[2] Worldwide HTN is estimated to cause 7.1 million premature deaths (6%) and 4.5% of disease burden.[3]

As per JNC-7 classification Stage -1 HTN is the one where systolic blood pressure (SBP) is 140-159 mmHg & diastolic blood pressure (DBP) is 90-99 mmHg.[4] Evidence suggests that reduction of blood pressure (BP) by 5 mmHg can decrease the risk of stroke by 34%, ischemic heart disease by 21%, and also reduce the likelihood of dementia, heart failure & mortality from cardiovascular disease.[5]

Several classes of antihypertensives are used to reduce BP. They differ in side effect profiles, ability to prevent endpoints & cost with availability. Among these, Angiostensin converting enzyme inhibitors (ACEIs) & Angiostensin receptor blockers (ARBs) are commonly & frequently used by most of the clinician to treat stage-1 HTN as first line of treatment. These drugs are found to have fewer side effects, low-cost & available in market. There is paucity of knowledge regarding antihypertensive effects, tolerability & compliance of use of these drugs in rural setting, so we have planned to carry out this study in a tertiary care hospital to see response of patients in rural & suburban people. We planned a comparative study to evaluate response of ACEIs & ARBs in uncomplicated stage-1 HTN among rural & suburban population in a rural setting.

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MATERIALS AND METHODS:

A randomized, single blind, parallel & cross over clinical study was conducted in Medicine out-patient department (OPD) of a tertiary care teaching hospital situated in rural area for a period of 12 months. Approval for study was obtained from Institutional Ethics Committee. Every effort was made to adhere to the Indian Council of Medical Research (ICMR) ethical guidelines for clinical research. Patients of both sexes, aged 25-60 years, who attended Medicine OPD with uncomplicated stage-1 HTN were included in study. Exclusion criterias were complicated & secondary hypertension, clinically significant laboratory abnormalities (e.g. electrolyte imbalance, increased urea/creatinine level etc.), patients receiving any drugs known to affect BP or medical treatment which can influence BP, allergy or contraindicated to ACEIs or ARBs, female with childbearing potential, history of drug abuse or alcohol consumption & patients participated in other clinical trial 3 months before screening.

Patients were checked & recruited for SBP/DBP in sitting posture. Written Informed Consent was taken from each participant. Patients put signature or thumb impression on consent form. Patients were randomly selected in 2 groups, where patients of 'even' number were taken into Group-A & patients of 'odd' number were taken into Group-B. Blood investigations-TC, DC, ESR, Hb%, random sugar, urea, creatinine, Na^+, K^+, lipid profile) & 12 leads E.C.G were checked during screening before prescribing medicine to each patients. Patients of Group-A were provided tab Ramipril (5mg/day) at start of treatment. They were advised to take medicine once daily. In first phase, it was continued for 6 weeks with scheduled follow up visits for BP check up and physical examination. It was followed by wash out period for 1 week[6] to remove the effect of first drug from the body. During wash out period, repeat blood & E.C.G were done. Following wash out period, patients were prescribed tab Losartan (50mg/day) for taking once daily for next 6 weeks with similar follow up visits. At the end of treatment, repeat blood & E.C.G were done to compare any changes in blood and E.C.G. Similarly the patients of Groups-B were given tab Losartan (50mg/day) once daily at initiation of treatment (for 6 weeks), after wash out period for 1 week, tab Ramipril (5mg/day) was prescribed for same duration(next 6 weeks) and scheduled follow up visits as in Group-A. Every time patients were checked/ examined for SBP & DBP in office sitting posture & were enquired about any adverse reactions or any problems related to study.

Above mentioned procedure were repeated in the same way only with exception that Group-A received tab Losartan & Group-B received tab Ramipril for another 6 weeks after a "Wash Out" period of 1 week at the beginning of 2nd course of treatment. Data were entered in Microsoft Excel and analysed using statistical software, namely SPSS for Windows version 17.0**.** Continuous efficacy variables were compared between groups by paired t test for comparison.

RESULT:

A total of 108 patients attending OPD at Medicine Department, with history or symptoms of HTN were included in study. Out of these, 100 (92.59%) patients completed the study as per modified intention-to-treat criterion specified in protocol – 50 in each group. Three subjects did not continue in Group-A due to either rash or rash with cough & five subjects in group-B, due to some ailment like fever or pain abdomen or without showing any reason.

Table 1: Demographic profile of the patients (N=108)

Parameter	**Frequency**		**Parameter**	**Frequency**	
Age (years)	**Gr-A**	**Gr-B**	**Sex**	**Gr-A**	**Gr-B**
30-35	2	3	Male	18	11
36-40	9	9	Female	35	44
41-45	7	10	**Residence**		
46-50	11	9	Urban	24	
51-55	12	10	Rural	84	
56-60	12	12	**Occupation**		
			Housewife	75	
			Agriculture	11	
Literacy status			Worker	10	
Literate	47		Service	7	
Illiterate	61		Business	4	

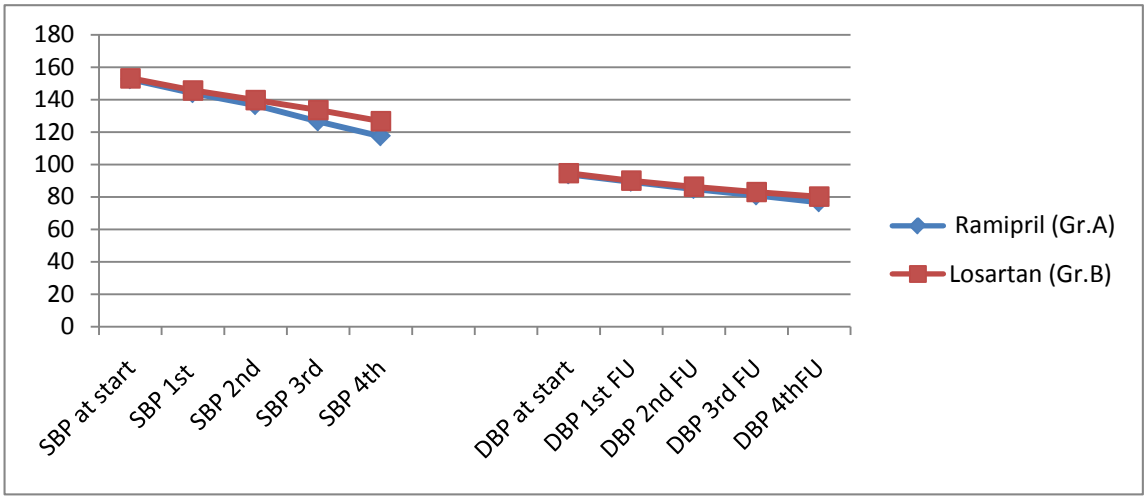

Figure 1: showing changes in SBP & DBP in mmHg from start up to 4th follow up in group-A & group-B (N=100).

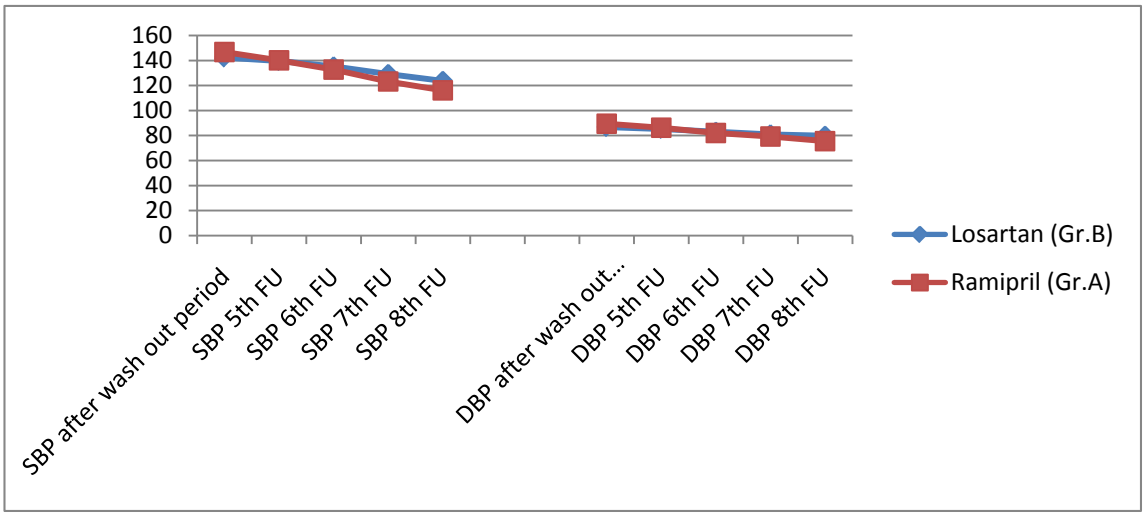

Figure 2: showing changes in SBP & DBP in mmHg after wash-out period up to 8th follow up in group-A & B (N=100).

Reduction of SBP is significantly (p<0.001) greater in case of tab. Ramipril (35±4.025 mmHg in group–A) than tab. Losartan (25±8.844 mmHg in group-B). Reduction of DBP is significantly (*p*<0.001) more in case of tab. Ramipril (17.24±4.009 mmHg in group-A) than tab. Losartan (14.44± 4.395 mmHg in group-B).

Table 2: shows difference in mean & standard deviation & other variables with respect to SBP & DBP in 1st phase of treatment between two groups.(N=100)

Paired Samples Test

Pair 1 A-B	Paired Differences					T	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
SBP	9.500	10.098	1.428	6.630	12.370	6.652	49	0.001
DBP	2.800	6.565	0.928	0.934	4.666	3.016	49	0.004

In group-B patients, in 2nd phase of treatment, reduction of SBP is significantly (p<0.001) more in case of tab. Ramipril (30.60±7.163 mmHg in group-B patients) than tab. Losartan (18.60±3.796 mmHg in group-A patients. Also reduction of DBP is significantly (p<0.001) more in case of tab. Ramipril (13.88± 4.008 mmHg in group-B patients) than tab. Losartan (6.88± 2.496 mmHg in group-A patients).

Table 3: shows difference in mean & standard deviation & other variables with respect to SBP in 2nd phase of treatment between two groups. (N=100)

Paired Samples Test

	Paired Differences							
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		T	df	Sig. (2-tailed)
Pair 1 A-B				Lower	Upper			
SBP	-12.000	7.548	1.068	-14.145	-9.855	-11.241	49	0.001
DBP	-7.000	4.853	0.686	-8.379	-5.621	-10.199	49	0.001

Table 4: showing mean ± standard deviation values of blood parameters (Na+, K+, random sugar, urea, creatinine, cholesterol, TG, HDL, VLDL, LDL) during course of treatment in Group-A & B patients respectively.

Blood parameters (Mean ± SD) in group A & B (N=100)

Parameters	**Time**	**Screening**		**Wash-out**		**End of treatment**	
	Group	**Gr-A**	**Gr-B**	**Gr-A**	**Gr-B**	**Gr-A**	**Gr-B**
Na^+		139.5± 3.3579	139.36± 2.9813	139.8 ± 3.1298	139.4 ± 2.9416	139.46 ± 3.2839	138.88 ± 2.662
K^+		4.048 ± 0.2013	4.084 ± 0.2469	4.034 ± 0.2353	4.112 ± 0.2173	4.044 ± 0.234	4.104 ± 0.2089
Random Sugar		84.5 ± 4.097	84.18 ± 6.14	85.78 ± 3.8188	86.6 ± 4.8781	86.7 ± 3.7648	87.72 ± 5.6244
Urea		28.48 ± 5.0112	27.3 ± 3.9757	27.76 ± 5.0732	27.34 ± 4.0938	27.52 ± 4.6653	27.12 ± 3.7992
Creatinine		0.76 ± 0.101	0.876 ± 0.1954	0. 746± 0.1034	0.876 ± 0.1779	0.76 ± 0.103	0.88 ± 0.16
Cholesterol		206.04 ± 37.676	183.52 ± 36.5	200.2 ± 33.74	191.56 ± 35.8	212.32 ± 39.69	201.72 ± 37.3
TG		159.82 ± 32.379	135.36 ± 39.70	171.52 ± 32.03	143 ± 31.028	162.02 ± 25.219	140.84 ± 26.63
HDL		46.66 ± 5.565	43.04 ± 6.34	46.46 ± 5.031	46.26 ± 5.945	44.64 ± 6.114	42.91 ± 6.067
VLDL		38.96 ± 10.646	30.22 ± 8.64	39.82 ± 8.547	36.4 ± 6.821	36.96 ± 7.401	31.48 ± 5.838
LDL		109.06 ± 34.786	108.62± 34.921	120.9 ± 29.952	118.68 ± 30.81	120.06 ± 33.23	116.28 ± 29.56

DISCUSSION:

HTN is an important modifiable risk factor for development of CVD throughout the world. HTN is treated by different classes of drugs in different individuals. ACEIs & ARBs are used more extensively as antihypertensives clinically. It has promoted & encouraged us to enter into research process to focus & find out which one is better efficacious & tolerable in treatment of uncomplicated stage-1 primary HTN with compliance of patients to drugs. Study was carried out among sub-urban & rural patients in tertiary care hospital, as this hospital drains patients mostly from rural

belt. It was 'single blind' study as study subjects were blind regarding change & type of antihypertensive medicines in their prescription during study period. It was 'parallel' and 'cross over' study as when tab. Ramipril was given in one group, then in another group, tab losartan was prescribed for first phase and it was reversed in second phase.

In our study, we choose wash-out period for 1 week because we considered that it would remove antihypertensive effects of the drug given in first phases from body. In case of Ramipril, plasma half-life ($t_{1/2}$) is 2-4hrs.[7] It was a prodrug & converted to active metabolite 'Ramiprilat' which has a long duration of action around 3-16 hrs. So, complete removal of effect of drug from body roughly requires 30-36 hrs (5t½) or 1-2 days. On the other hand, Losartan has plasma half-life (t½) of 1.5-2 hrs.[8] But it undergoes significant first-pass metabolism to produce 5-carboxylic acid metabolite. This metabolite is a long-acting (6 -8 hr), non-competitive antagonist at the AT_1 receptor & contributes to the effects of Losartan. So, complete removal of effects of Losartan from body roughly requires 24-30hrs ($5t_{1/2}$) or 2-3days. Not only that but also in OPD of such kind of overloaded hospital, it was quite inconvenient to review patients at interval of 3-4days, rather it was convenient for patients to come after one week on the same day for follow up. In ESPORT STUDY[9] wash-out period was fixed for 2 weeks with placebo, which was in contrast with our study.

In our study, we used fixed dose preparation in both drugs to observe & compare the antihypertensive effects at that particular dose in stage-1 HTN. We prescribed tab Ramipril in a dose of 5mg/day & tab Losartan 50mg/day. But in various studies, these drugs were used in fixed dose alone[10,11] or titrated doses [12,13] & obtained significant results. Patients had to purchase medicines as these were not available in hospital or sponsored by anyone. They purchased these medicines in fixed brand name (Ramipril- 'Macpril'; Losartan- 'Losar') from local market & low cost than other bands available locally as seen by local market surveillance.

In this study, it was found that patients affected with HTN were between 40-60 years but most affected was 56-60 years in both groups & mean age of patient was about 48.71years. In LORD Trial[10] mean age of patient was 52.93 years where range of affected persons was 45-60years. In that study, 62.86% was male and 37.14% female. In our study, 73.14% were female and 26.85% were male out of total 108 patients. Reason behind this might be due to higher attendance of female patients at OPD in hospital in comparison to male patients or it might be due to higher prevalence of HTN in females in the community of study areas though we did not have any supportive evidence for this. Occupationally, 69.44% patients were house wife, 10.18% were involved in agriculture, 9.25% workers in different sectors, 6.48% engaged in service and 3.70% in business. It was noted that a large portion of the affected patients were housewife & it might be due to their extreme age, sedentary activity & food habits. From point of view of residence, 77.77% study population was from rural & suburban areas & 22.22% from urban areas. Our study did not find any variation in the result i.e. in reduction of BP due to occupational and residential variation in study subjects. Among study populations, 56.48% patients were literate & 43.51% patients illiterate but literacy was found to had no direct impact on study result, as almost all patients were regular in taking their prescribed medicines due to therapeutic benefits of antihypertensive drugs. The investigator did not find any studies where demographic characteristics had affected the result.

In our study, in group-A patients, tab Ramipril reduced mean SBP & DBP significantly more than group-B in 1st phase of treatment. Similarly in 2nd phase of treatment, there was significant reduction of mean SBP & DBP more in group-B by Ramipril than group-A by Losartan. Statistically, our study had got almost similar results like other studies [10,11,14,15] that Ramipril & Losartan reduced both SBP & DBP significantly ($p<0.001$) in both group of patients & this study also observed that, mean reductions of SBP and DBP were more in case of Ramipril than Losartan.

In this study, no significant alterations in blood levels of random sugar, urea, creatinine or Na+/K+ were found by the investigator. Not only that but also no significant changes were found in different lipid levels (TGs, Cholesterol, VLDL, LDL & HDL) in pre and post-treatment values in any groups. The investigator observed these findings were matched like other studies [12, 16].

Study was also to assess tolerability of patients to drugs given to them during entire course of treatment. In general, most patients of both Groups showed good tolerability to both tab Ramipril & tab Losartan**.** In group-A, three patients who started with tab.Ramipril discontinued their treatment due to either rash, or cough with rash which was about 2.78% out of 108 patients and in group-B, five patients who started with tab.Losartan discontinued their treatment due to some nonspecific complaints like pain abdomen and fever etc, which was about 4.62%. Out of 108 patients, rate of withdrawal from treatment was 7.40%. In other studies [10, 17], it was observed that 98.41% were tolerable to both of these drugs. Study was also to assess compliance which showed

good compliance among patients of both groups[18] as they were strictly attached to their prescribed medicines during course of treatment due to beneficial effects of antihypertensive drugs; although few patients withdrew themselves from study due to related ailments. We prescribed brand of 'Macpril 'for Ramipril & cost was Rs.81/- for 10 tablets i.e. Rs. 8.10/- was expensed by patients for 1 tablet per day. On other hand, brand 'Losar' was given for Losartan and cost was Rs.57/- for 10 tablets i.e. 5.70/- was expensed by patients for 1 tablet per day. The cost difference between two drugs was only Rs.2.40/- per tablet per day where 'Macpril' was little costly than 'Losar.' However, costs of both drugs were quite affordable to patients in both groups. Probably due to low cost of drugs, patients took medicine regularly & their compliance was good during entire course of study period.

Limitation of study:

It was a small study as it dealt with almost single parameter. We did not take body weight of patients and doses of drugs were not prescribed as per body weight. Therefore, effects of drugs could not be tallied with body weight. We took baseline blood level parameters but did not consider any changes of biomarkers or metabolic effects of drugs (Adiponectin, high-sensitivity C-reactive protein, matrix metalloproteinase-2 & 9 etc). We did not take into our considerations changes regarding insulin sensitivity, protein level in urine. Any changes in blood vessel endothelial function due to effects of drugs were not considered by us. Our study was only limited to uncomplicated stage-1 essential hypertension and unable to show any alterations in the effects in secondary hypertension.

CONCLUSION:

In our study, we observed that both the drugs tab. Ramipril & tab. Losartan reduced SBP and DBP gradually from baseline BP in both groups of patients but Ramipril reduced more effectively and significantly ($p<0.001$) both SBP & DBP than Losartan. Hence Ramipril had better efficacy than Losartan in reduction of BP in stage-1 HTN patients with no complications, though it is slightly costlier.

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