Internet Journal of Medical Update

Journal home page: http://www.akspublication.com/ijmu

Original Work

A comparative evaluation of Losartan/Hydrochlorothiazide (fixed combination) versus Amlodipine monotherapy in patients with hypertension in Rohilkhand region

Iram Shaifali*, AK Kapoor*Ψ, HK Singh* and RK Patial**

***Department of Pharmacology, **Department of Medicine, Rohilkhand Medical College, Bareilly, UP, India**

(Received 06 October 2013 and accepted 21 March 2014)

ABSTRACT: The aim of this prospective randomized study is to comparatively evaluate the antihypertensive efficacy of combination therapy (losartan/hydrochlorothiazide) with monotherapy (amlodipine). This prospective randomized clinical study was carried out for twelve months (July 2012 – June 2013) and enrolled 250 newly diagnosed stage-I hypertensive patients (as per JNC-7 criteria), who attended medicine outdoor department of Rohilkhand Medical College & Hospital, Bareilly. Hypertensive patients between 18 - 70 years of age were included in the study. The patients were randomly divided into two groups. The Losartan / Hydrochlorothiazide (LST/HCTZ) group included 128 patients and amlodipine group (AMLO) included 122 patients. A total of 40 patients, 14 patients of LST/HCTZ group and 26 patients of AMLO group dropped out during the study. M/F ratio was 0.92:1, and urban/rural ratio was 1.06:1. Majority of patients were in the 41-50 years age group. Mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) were comparable between both groups, being 152.97 mm Hg and 95.05mm Hg for LST/HCTZ group and 153.27mm Hg and 95.27 mm Hg for AMLO group. Both mean SBP and mean DBP blood were statistically significantly reduced in each of the six follow ups in both the groups ($p<0.001$). The mean SBP was reduced from 152.97±0.45 to 121.65±0.81 and mean DBP was reduced from 95.05±0.17 to 76.28±0.51(in the sixth follow-up) in LST/HCTZ group. Similarly mean baseline SBP 153.270±64 was reduced to 120.65±0.93 and mean baseline DBP was reduced from 95.270±38 to 75.54±0.67 after six months of therapy in AMLO group. The comparative evaluation of the two regimens revealed no statistically significant difference ($p>0.05$) in both SBP and DBP reduction. Both LST/HCTZ and AMLO regimen were equally effective and well tolerated in lowering blood pressure.

KEY WORDS: ***Anti-hypertensive efficacy, Losartan/ hydrochlorothiazide combination, Amlodipine; Hypertensive patients***

INTRODUCTION

Affecting a population of one billion worldwide, hypertension has become the most common, readily identifiable and reversible risk factor for myocardial infarction, stroke, heart failure, atrial fibrillation, aortic dissection and peripheral arterial disease.[1] The selection of first-line antihypertensive agents must be based not only on efficacy and outcome, but also on tolerability and compliance, which includes both quality of life considerations and cost. Thiazide diuretics and calcium channel blockers (CCBs) are effective, as well as combinations that include renin angiotensin-aldosterone system (RAAS) blockers in reducing BP. Amlodipine besylate (AMLO) is a long-acting dihydropyridine calcium antagonist whereas losartan potassium (LST) is an angiotensin II type 1 receptor antagonist; both these agents are currently being used in hypertension. Adding small doses of

ΨCorrespondence at: Professor, Department of Pharmacology, Rohilkhand Medical College, Bareilly, UP, India; Phone: +919415373166; Email: drakkapoor@rediffmail.com

hydrochlorothiazide (HCTZ) to losartan increases the antihypertensive efficacy of the latter drug.[2]
There have been several studies comparing the antihypertensive efficacy and tolerability of a fixed combination of losartan (LST) and hydrochlorothiazide (HCTZ) with those of amlodipine besylate (AMLO) in westerners.[3,4] However, data in Asians are scarce, who have been reported to respond more favorably to calcium channel blockers and less favorably to angiotensin-converting enzyme inhibitors as compared to westerners.[5]
The aim of the present study is to comparatively evaluate the antihypertensive efficacy and tolerability of a combination therapy, using a fixed combination of LST and HCTZ with monotherapy using AMLO, in patients of hypertension, conforming to JNC-7 criteria.

METHODOLOGY

A prospective, randomized clinical study of one-year duration (July 2012 – June 2013) was carried out in the department of pharmacology with the collaboration of the medicine department in Rohilkhand Medical College and Hospital, Bareilly. Ethical clearance from the institutional ethical committee was obtained. Written informed consent from all participants was taken.
A total of 250 newly diagnosed hypertensive patients conforming to stage 1 JNC-7 criteria who were 18 years and above, of both sexes, attending the medicine outdoor department were included and constituted the sample. 128 patients were enrolled in LST/HCTZ group and 122 patients in the AMLO group. Patients of secondary hypertension, patients with impaired liver and/or kidney function, pregnant and lactating females and those taking oral contraceptive pills were excluded from the study.
The study involved the use of a structured, pretested and predesigned questionnaire to collect the demographic information and the patient's blood pressure was measured with standardized calibrated mercury column type sphygmomanometer and stethoscope using standard protocol as per American Heart Association recommendations.
All newly diagnosed cases of hypertension were randomly divided into two groups. The first group was treated with Losartan/Hydrochlorothiazide (LST/HCTZ) 50/12.5mg once daily and the second group received Amlodipine besylate (AMLO) 5mg once daily throughout the study. Laboratory tests like random blood glucose (RBS), urine (routine and microscopic), serum creatinine, serum uric acid, serum potassium, serum bilirubin and lipid profile were carried out before the initiation of therapy and after six months of completion of treatment. Patients under treatment were subsequently monitored and reassessed at 2 weeks (first follow up) then at 4 weeks (second follow up), 8 weeks (third follow up) at 12 weeks (fourth follow up) then at 18 weeks (fifth follow up), and then at 24 weeks (sixth follow up), for evaluation of BP reduction or control.
Statistical analysis was done by using the Microsoft Excel and SPSS windows version 14 software. The analyzed data was presented as Mean ± Standard Error of Mean (SEM). A p-value less than 0.05 were considered statistically significant.

RESULT

Out of 250 newly diagnosed hypertensive patients conforming to stage-1 JNC-7 criteria, 14 patients (10.9%) in LST/HCTZ group and 26 patients (21.3%) in Amlodipine (AMLO) group dropped out during the study. A higher prevalence of hypertension was noted in females (52%) compared to males (48%) in our study. M:F ratio was 0.92:1. The urban-rural ratio was 1.06:1 suggesting higher prevalence in urban patients. Mean SBP was 152.97 and 153.27 mm of Hg in LST/HCTZ group and AMLO group respectively. Similarly Mean DBP was 95.05 and 95.27 mm of Hg in LST/HCTZ group and AMLO group respectively. (**Table 1**)

Table 1: Demographic features of hypertensive patients

S.N.		LST/ HCTZ	AMLO	TOTAL
1	**Male**	66	54	120
2	**Female**	62	68	130
3	**Rural**	59	62	121
4	**Urban**	69	60	129
5	**Mean SBP**	152.97	153.27	
6	**Mean DBP**	95.05	95.27	

LST- Losartan; HCTZ- Hydrochlorothiazide; AMLO- Amlodipine besylate

Table 2 depicts age and education distribution of enrolled patients. An increasing trend of hypertension was noted with increasing age. Majority of patients were in the age group of 41-50 years. 121 (48.4%) hypertensive patients were illiterate. A total of 48 patients were educated up to middle school (8th standard), whereas 20 were high school graduates and 28 were post graduate/professionals.
After therapy with LST/HCTZ, in all the subsequent six follow-ups the mean SBP and mean DBP were statistically significantly reduced ($p<0.001$) as compared to baseline mean SBP and mean DBP (**Table3, 4**). Similarly following therapy with amlodipine in all the six follow-ups

the mean SBP and mean DBP were statistically significantly reduced (p<0.001) when compared with baseline mean SBP and mean DBP (**Table 5, 6**).

Table 7 depicts comparative evaluation of SBP and DBP with the two regimens. SBP showed a significant reduction from baseline to the end of treatment. It was noted that SBP reduced at six month by 31.32 mmHg {95% CI: (29.54 to 33.10)} in LST/HCTZ group and by 32.62mm Hg {95% CI: (31.48 to 35.76)} in Amlodipine group (p<0.001 for both groups). However, the difference in mean reduction of SBP between the two groups was not statistically significant (p = 0.25) with the degree of freedom being 208 following six months of therapy. Similarly DBP showed a statistically significant reduction from baseline to the end of the treatment in both the regimens (p<0.001 for both groups). It was further observed that DBP was significantly reduced at six months by 18.77mmHg {95% CI: (17.75 to 19.79)} in the LST/HCTZ group and by 19.73 mmHg {95%CI: (18.28 to 21.18)} in the AMLO group. However the difference in the mean reduction of DBP between the two groups was not statistically significant (p = 0.16).

Table 2: Age and education wise distribution of patients

SN	AGE	LST/HCTZ	AMLO	Total	Education Status	LST/HCTZ	AMLO	Total (%)
1	18-30	8	16	24	Illiterate	65	56	121 (48.4%)
2	31-40	35	24	59	Upto middle school	28	20	48 (19.2%)
2	41-50	42	43	85	high school	13	19	32 (12.8%)
4	51-60	37	30	67	graduate	10	11	21 (8.4%)
5	> 61	6	9	15	postgraduates/ professionals	12	16	28 (11.2%)
	Total	128	122	250	Total	128	122	250 (100%)

Table 3: SBP changes with LST/HCTZ regimen

BASELINE (Mean SBP±SEM)	Follow up (Mean SBP±SEM)	t-value	df	p-value
0 152.97±0.45	1 146.13±0.59	9.19	127	<0.001 Significant
0 152.97±0.45	2 139.53±0.65	16.93	127	<0.001 Significant
0 152.97±0.45	3 130.35±0.59	30.69	113	<0.001 Significant
0 152.97±0.45	4 124.91±0.61	37.28	113	<0.001 Significant
0 152.97±0.45	5 122.95±0.62	39.55	113	<0.001 Significant
0 152.97±0.45	6 121.65±0.81	34.59	113	<0.001 Significant

Table 4: DBP changes with LST/HCTZ regimen

BASELINE (Mean DBP±SEM)	Follow up (Mean DBP±SEM)	t-value	df	p-value
0 95.05±0.17	1 89.88±0.31	14.14	127	<0.001 Significant
0 95.05±0.17	2 85.78±0.38	21.65	127	<0.001 Significant
0 95.05±0.17	3 81.3±0.43	30.28	113	<0.001 Significant
0 95.05±0.17	4 79.3±0.38	38.49	113	<0.001 Significant
0 95.05±0.17	5 78.11±0.38	41.70	113	<0.001 Significant
0 95.05±0.17	6 76.28±0.51	36.32	113	<0.001 Significant

Table 5: SBP changes with AMLO regimen

Baseline (Mean SBP±SEM)	Follow up (Mean SBP±SEM)	t-value	df	p-value
0 153.27± 0.64	1 145.27± 0.56	9.48	121	<0.001 Significant
0 153.27± 0.64	2 138.84± 0.75	14.89	121	<0.001 Significant
0 153.27± 0.64	3 129.66± 0.88	22.21	113	<0.001 Significant
0 153.27± 0.64	4 123.6± 0.72	30.64	105	<0.001 Significant
0 153.27± 0.64	5 121.98± 0.72	32.31	95	<0.001 Significant
0 153.27± 0.64	6 120.65± 0.93	29.49	95	<0.001 Significant

Table 6: DBP changes with AMLO regimen

Baseline (Mean DBP±SEM)	Follow up (Mean DBP±SEM)	t-value	df	p-value
0 95.27± 0.38	1 89.73± 0.35	10.65	121	<0.001 Significant
0 95.27± 0.38	2 85.89± 0.46	15.71	121	<0.001 Significant
0 95.27± 0.38	3 80.41± 0.48	24.43	113	<0.001 Significant
0 95.27± 0.38	4 78.41± 0.48	27.88	105	<0.001 Significant
0 95.27± 0.38	5 76.95± 0.58	27.08	95	<0.001 Significant
0 95.27± 0.38	6 75.54± 0.67	26.83	95	<0.001 Significant

Table 7: Comparative reduction of SBP and DBP after six months therapy with two regimens

	SBP		Reduction from baseline	Difference	p value
	Baseline	**6 months**			
LST/HCTZ	152.97±0.45	121.65±0.81	-31.32{95% CI: (29.54 to 33.10)}	-1.30{95% CI: (-3.55 to 0.95)}	p=0.25
AMLO	153.27±0.62	120.65±0.93	-32.62{95% CI: (31.48 to 35.76) }		
	DBP		**Reduction from baseline**	**Difference**	**p value**
	Baseline	**6 months**			
LST/HCTZ	95.05±0.17	76.28±0.51	-18.77{95% CI: (17.75 to 19.79)}	-0.96{95% CI: (-2.30 to 0.38)}	p=0.16
AMLO	95.27±0.38	75.54±0.67	-19.73{95%CI: (18.28 to 21.18)}		

DISCUSSION

Affecting 1 billion people the world over, hypertension remains one of the leading causes of death worldwide thus making it a public health problem.[6] Although, a wide variety of anti-hypertensives belonging to different pharmacological classes and targeting different physiological components of BP are being used for the management of hypertension, yet in the present study only two different groups of agents (LST/HCTZ and AMLO) were used for comparative evaluation between combination therapy versus monotherapy because of their efficacy, and that these chosen groups of agents in the doses applied cause minimal adverse effect profile. Moreover, they are well tolerated and quite effective in Asian populations.

A total of 40 patients, 14 in LST/HCTZ group and 26 in AMLO group dropped out during the study period because of adverse effects, lack of compliance, cost of medicine and more importantly due to poor awareness that despite the controlled BP one has to take medicine almost throughout his/her life.

In the present study, the two groups (LST/HCTZ and AMLO group) are well matched with regard to initial systolic and diastolic blood pressures for proper comparative evaluation. The M:F ratio in the present study is 0.92:1 showing that females predominate over males. This is in line with observations reported in the serial epidemiological studies conducted in Jaipur by Gupta et al[7,8] where the prevalence of hypertension was lower (30% and 36% respectively) among males as compared to (34% and 38%) respectively) in females.

The prevalence of hypertension is more in the urban population (51.6%) compared to the rural population (48.4%). Earlier workers in the field[9-11] have reported a similar trend. These observations in respect to urban population are probably due to adoption of western lifestyles, exposure to higher stressful conditions, consumption of junk fast foods and increased life expectancy with sedentary habits.

In the present study, increasing age is associated with increasing prevalence of hypertension and majority of patients belonged to the age group of 41-50 years. These observations are corroborative with those of other studies.[12-15] Rising atherosclerotic changes in vascular systems with increasing age may be the prime cause.

The incidence of hypertension is slightly more (51.6%) in literate individuals compared to illiterates. This is probably attributable to a greater awareness amongst the literate population. It is of interest that prevalence of hypertension is much higher amongst postgraduates/professionals (11.2%). Gopinath et al[9] has also reported a similar observation related to lifestyle changes and stressful working conditions.

In the present study, baseline mean SBP and the mean DBP are 152.97 mmHg and 95.05 mmHg for LST/HCTZ group and 153.27 mmHg and 95.27mmHg for AMLO group respectively. Other researchers[16-18] in the field also reported similar baseline values of SBP and DBP. It is observed that following treatment, SBP is consistently and significantly decreased in each of the six follow-ups when compared to baseline SBP (statistically significant $p<0.001$, t value 34.59, df 113) in LST/HCTZ group patients.. Our findings in respect to SBP changes are consistent with other researchers[16-20], who have also observed a statistically significant reduction in SBP thoroughout their study periods.

Regarding changes in DBP following LST/HCTZ combination therapy, there is a consistent fall in DBP in all six follow-ups. The onset of action is quite early in therapy at 2 weeks. The association between the baseline DBP values and the drug treated values in all the six follow-ups are statistically significant ($p<0.001$). These observations are consistent with previous studies[16-20]. This clearly suggests that combination therapy with LST/HCTZ produced a significant reduction in BP in stage-1 hypertensive patients and is highly effective. Thus, it is observed that both SBP and DBP are decreased significantly with LST/HCTZ therapy at 2 weeks of initiation of therapy and reduction in BP continued through out all the six follow-ups. This observation contradicted the findings of a previous study, where reduction in BP by losartan alone was not observed before six weeks and may be delayed for up to 12 weeks, and combination therapy with LST/HCTZ did not show an early effect.[19]

Regarding the effects of AMLO group (a long acting Ca++ antagonist) on SBP, it is observed that there is highly significantly reduction in SBP ($p<0.001$) at the first follow-up and all six subsequent follow-ups. It is observed that there is a reduction in DBP which is statistically highly significant ($p<0.001$). Moreover, the onset of action (reduction in BP) is noted quite early in both SBP as well as DBP. Thus monotherapy with AMLO is highly effective and efficacious for reduction of both SBP and DBP in hypertensive patients. Wilson et al[19] observed that both losartan and amlodipine reduced the sitting DBP and sitting SBP after six weeks of therapy thus contradicting our observation of an early onset of action by amlodipine. Our findings in respect to changes in SBP and DBP with AMLO monotherapy are concurring with these of other workers[16,18,21] who observed a substantial decrease in SBP and DBP in respect to baseline values.

The comparative evaluation in respect to changes in mean SBP with LST/HCTZ combination therapy with that of AMLO monotherapy has shown a consistent fall at each of subsequent follow-ups, being ultimately reduced to 121.65 mmHg at the sixth follow-up in LST/HCTZ group and to 120.65 mmHg in the AMLO group. Hence, it is noted that although both regimens individually produced statistically highly significant reduction in SBP ($p<0.001$ for both groups) yet there is no statistically significant difference ($p<0.05$) when mean values of SBP of both regimens are compared at each follow-up. It was further noted that SBP reduced at six months by 31.32 mmHg {95% CI: (29.54 to 33.10) N=114} in LST/HCTZ group and by 32.62 mmHg {95% CI: (31.48 to 35.76) N=96} in amlodipine group ($p<0.001$ for both groups). However, the difference in the mean change of SBP between these two groups was not significant {-1.30 mmHg (95% C1: -3.55 to 0.95) p=0.25}. Our findings are in concurrence with those of Chung et al[18] who have reported that SBP is significantly reduced from the baseline to the end of treatment (12 weeks), by 19.7 mmHg (95% C1: 17.0 to 22.4) in LST/HCTZ group and by 19.2 mmHg (95% C1: 16.5 to 21.9) in amlodipine group ($p<0.001$ for both groups). However, the difference in the mean change of SBP between the two groups was not significant {-0.5mmHg (95% C1: -4.3 to 3.4), P=0.82}. Our findings of comparative SBP changes with the two regimens are also in line with those of Wilson et al[21] but contradicted those of Philips et al[16] who observed a statistically significant ($p = 0.018$) greater reduction from the baseline in SBP in the amlodipine group throughout the study period.

Regarding comparative evaluation of the two regimens with respect to reduction in DBP, it is observed that the fall in DBP (onset of action) is quite early in AMLO group probably due to a potent vasodilator action. Further, both the regimens individually produced statistically significant reductions in DBP ($p<0.001$ for both groups) yet there is no statistically significant difference ($P>0.05$) when the mean values of DBP of both the regimens are compared at each follow-up. It was further observed that DBP was significantly reduced at six months by 18.77 mmHg {95% CI: (17.75 to 19.79) N=114} in the LST/HCTZ group and by 19.73 mmHg {95% CI: (18.28 to 21.18) N=96} in the AMLO group. However the difference in the mean reduction of DBP between the two groups was not statistically significant {-0.96 mmHg (95% C1: -2.30 to 0.38) p = 0.16}. Our findings corroborate those of Chung et al[18] who has reported that DBP had been significantly reduced at the end of the study by 11.6 mmHg (95% C1: 10.1 to 13.2) in the LST/HCTZ group and by 12.8 mmHg (95% C1: 11.2 to 14.4) in AMLO group ($p<0.001$ for both groups). However the difference in the mean change of DBP between the two groups is not statistically significant (1.2 mm Hg (95% C1: -1.1 to 3.4), p = 0.31). Other researchers[19,22] also reported similar findings in respect to comparative reduction in DBP in the LST/HCTZ and AMLO groups. However, our findings are contradictory to those of Philips et al[16] who observed that the mean change in DBP from the baseline to the end of treatment was statistically significantly greater in the amlodipine group (-12.6 mmHg, N = 218) than in the LST/HCTZ group (-10.3 mmHg; N = 222) (p= 0.002).

It is observed that the number of patients attaining the goal BP/normotension (<140/90 mm Hg) is comparable between the two regimens and there is no significant difference in response rates between the LST/HCTZ group (71.05%) and the AMLO

group (73.9%) (p = 0.64). These findings are similar to various other studies[16-19,21,23].

Our findings in respect to equal efficacy of the two regimens are in line with those of LOA study group[4] who concluded in their study that both LST/HCTZ and AMLO lowered BP equally well, better than 50 mg or 100 mg losartan alone. Our findings are also in line with the observations of various other studies[16-19,21]. Earlier studies have reported that losartan potassium alone causes a fall in BP after 6 weeks or more but our findings suggest that addition of HCTZ to losartan results in faster onset of action (BP lowering effect) compared to LST alone.

Thus, it can be noted that a comparison between combination therapy with fixed combination of LST/HCTZ group in low dose and monotherapy with low dose amlodipine has yielded no statistically significant reduction of BP. This is in contradiction to the conventional belief that combination therapy usually produces a better clinical outcome. This is owing to the fact that in certain clinical situations and clinical designs such as here, where only stage-1 hypertensive cases (as per JNC 7 criteria) were included as test subjects and two different groups of anti-hypertensive drugs were compared, this type of anomaly in respect to clinical outcome may be observed. However, it may be pointed out that only when combination therapy (LST/HCTZ) is compared with same group of drug (LST alone) then combination therapy will definitely produce an enhanced anti-hypertensive effect and will justify reduction in dose, as also, one drug may oppose the side effects of another.

In conclusion, both low dose LST/HCTZ combination therapy and monotherapy with AMLO regimen are equally effective in lowering raised BP and are well tolerated. Moreover, combination therapy produces a rapid reduction of BP even in a low dose. Although AMLO caused a greater reduction in SBP and DBP as compared to LST/HCTZ, the difference is not statistically significant.

REFERENCES

1. Victor RG. Systemic hypertension: mechanisms and diagnosis. Braunwald's Heart Disease: A textbook of cardiovascular medicine. Eds: Bonow RO, Mann DP, Zipes DP, Libby P. 9th ed, 2012:935-54.
2. MacKay JH, Arcuri KE, Goldberg AI, Snapinn SM, Sweet CS. Losartan and low-dose hydrochlorothiazide in patients with essential hypertension. A double blind placebo controlled trial of concomitant administration compared with individual components. *Arch Intern Med*. 1996;156(3):278-85.
3. Martina B, Dieterle T, Weinbacher M, Battegay E. Effects of losartan titrated to losartan/hydrochlorothiazide and amlodipine on left ventricular mass in patients with mild-to-moderate hypertension: A double-blind randomized controlled study. *Cardiology*. 1999;92(2):110-4.
4. Dahlof B, Lindholm LH, Carney S, Pentikainen PJ, Ostergren J. Main results of the losartan versus amlodipine (LOA) study on drug tolerability and psychological general well-being. LOA Study Group. *J Hypertens*.1997;15(11):1327-35
5. Jamerson K, DeQuattro V. The impact of ethnicity on response to antihypertensive therapy. *Am J Med*. 1996;101(3A):22S–32S
6. Fields LE, Burt VL, Cutler JA, Hughes J, et al. The burden of adult hypertension in the United States 1999 to 2000: a rising tide. *Hypertension*. 2004; 44(4):398-404.
7. Gupta R, Prakash H, Majumdar S, Sharma S, et al. Prevalence of coronary heart disease and coronary risk factors in an urban population of Rajasthan. *Indian Heart J*. 1995; 47(4):331-8
8. Gupta R, Gupta VP, Sarna M, Bhatnagar S, et al. Prevalence of coronary heart disease and risk factors in an urban Indian population: Jaipur Heart Watch-2. *Indian Heart J*. 2002; 54(1):59-66
9. Gopinath N, Chadha SL, Shekhawat S. Urban-rural differences in the prevalence of coronary heart disease and its risk factors in Delhi. *Bull World Health Organ*. 1997;75(1):31-8
10. Padmavati S, Gupta S. Blood pressure studies in rural and urban group in Delhi. *Circulation*. 1959;19(3):395-405
11. Gupta R. Trends in hypertension epidemiology in India. *J Hum Hypertens*. 2004;18(2):73-8
12. Sidhu S, Kumari K, Prabhjot. Socio-demographic variables of hypertension among adult Punjabi females. *J Hum Ecol*. 2005;17(3):211-5
13. Mehan MB, Srivastav N, Pandya H. Profile of non communicable disease risk factors in an Industrial setting. *J Postgrad Med*. 2006;52(3):167-71.
14. Deshmukh PR, Gupta SS, Dongre AR, Bharambe MS, et al. Relationship of anthropometric indicators with blood pressure levels in rural Wardha. *Indian J Med Res*. 2006;123(3):657-64
15. Prasanth TS, Vijayakumar K. Prevalence of systemic hypertension among the rural residents of Kerala. *Calicut Med J*. 2008;6(3):1-4
16. Phillips RA, Kloner RA, Grimm RH Jr, Weinberger M. The effects of amlodipine compared to losartan in patients with mild to moderately severe hypertension. *J Clin Hypertens*. 2003; 5(1):17-23
17. Minami J, Abe C, Akashiba A, Takahashi T, et al. Long-term efficacy of combination therapy

with losartan and low-dose hydrochlorothiazide in patients with uncontrolled hypertension. *Int Heart J*. 2007; 48(2):177-86

18. Chung JW, Lee HY, Kim CH, Seung IW, et al. Losartan/hydrochlorothiazide fixed combination versus amlodipine monotherapy in Korean patients with mild to moderate hypertension. *Korean Circ J*. 2009;39(4):151-5.
19. Wilson TW, Lacourcière Y, Barnes CC. The antihypertensive efficacy of losartan and amlodipine assessed with office and ambulatory blood pressure monitoring. *CMAJ*. 1998;159(5):469-76
20. Hosoya T, Kuriyama S, Ohno I, Kawamura T, et al. Antihypertensive effect of a fixed-dose combination of losartan/hydrochlorothiazide in patients with uncontrolled hypertension: a multicenter study. *Clin Exp Nephrol*. 2012;16(2):269-78
21. Oparil S, Barr E, Elkins M, Liss C, et al Efficacy, tolerability, and effects on quality of life of losartan, alone or with hydrochlorothiazide, versus amlodipine, alone or with hydrochlorothiazide, in patients with essential hypertension *Clin Ther*. 1996;18(4):608-25.
22. Wu SC, Liu CP, Chiang HT, Lin SL. Prospective and randomized study of the antihypertensive effect and tolerability of three antihypertensive agents, losartan, amlodipine and lisinopril, in hypertensive patients. *Heart Vessels*. 2004;19(1):13-8
23. Volpe M, Junren Z, Maxwell T Rodriguez A, et al. Comparison of blood pressure lowering effects and tolerability of losartan- and amlodipine-based regimens in patients with isolated systolic hypertension. *Clin Ther*. 2003;25(5):1469-89.