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Study of the Effect of Amlodipine, Atenolol, Enalapril and Losartan in Patients with Mild to Moderate Hypertension

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ABSTRACT

Objectives: *To evaluate and compare the efficacy and tolerability of amlodipine, atenolol, enalapril and losartan in patients with mild to moderate hypertension.*

Research design and method: *This study was conducted in medicine department of tertiary care teaching hospital. This was prospective, open labelled, observational, randomized controlled clinical trial. Patients aged 30-60 years, newly diagnosed as mild to moderate hypertension were enrolled in the study. Pretreatmentevaluation of all the patients was done. Detailed clinical history, physical examination and routine laboratory investigations were done. Eligible patients were randomized to receive Amlodipine 2.5/5 mg, Atenolol 25/ 50 mg, Enalapril5/ 10 mg, Losartan 25/50 mg and followed them for 12 weeks, patient'svisits scheduled at 2 weeks interval. Primary efficacy end point was reduction in mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP). Safety was assessed in terms of systemic adverse events both subjective and objective (clinical and biochemical examinations).*

Results: *Total 154 patients were enrolled, patients' demographic and baseline clinical characteristics were comparable in all treatment groups. After 12 weeks of treatment the reduction in mean systolic blood pressure were 22.55±7.74, 21±7.94, 20.35±5.48, 22.61±8.41. Reduction in mean diastolic blood pressure were 13.11±4.31, 10.11±3.24, 11.5±3.39, 12.72±3.38. The change in heart rate was 84.22 ± 5.71 to 85.56 ± 5.81, 83.27 ± 5.72 to 69.05 ± 7.68, 84 ± 6.17 to 85.72±5.47, 82.33 ± 7.15 to 83.5±7.54. The change in average serum potassium levels 3.81 ± 0.39 to 3.79 ± 0.36, 3.79 ± 0.33 to 3.69 ± 0.22, 3.72 ± 0.35 to 4.08 ± 0.38, 3.74 ± 0.40 to 3.81 ± 0.27. Adverse events percentage was 38.88 percent, 36.11 percent, 36.11 percent and 13.88 percent in all 4 study group respectively.*

Conclusion: *Amlodipine, Atenolol, Enalapril, and Losartan are equal efficacious to reduce SBP and DBP, whereas losartan is better tolerated and comparatively safer than amlodipine, atenolol and enalapril in patients with mild to moderate hypertension.*

Keywords: *Amlodipine, Atenolol, Enalapril, Losartan.*

1. INTRODUCTION

Hypertension is a major contributor to premature morbidity and mortality. Compared with other known risk factors for acute myocardial infarction, heart failure, stroke, end stage renal disease, hypertension is perhaps the simplest to diagnose, easiest to treat and one of the most cost effective preventive strategies [1].

The risk of atherosclerotic coronary heart disease is related to the increased levels of systolic and diastolic blood pressure. The prevalence of left ventricular hypertrophy increases with age and is higher in patients with hypertension. [2].

It has long been recognized that mortality and morbidity increase as both systolic and diastolic blood pressure rise and that in individuals over age 50, the systolic blood pressure is a better predictor of complications [3].

Hypertension can be classified as either essential hypertension indicates that no specific medical cause can be found to explain a patient's condition.

About 90-95% of hypertension is essential hypertension [4].

Losartan blocks angiotensin II binding to the type 1 receptor and blocks angiotensin II mediated vasoconstriction, aldosterone release and cellular growth [5].The anti-inflammatory and anti-oxidant effects which are probably due to unopposed stimulation of angiotensin II type 2 receptors may be beneficial in the prevention of cardiovascular disease in middle aged persons in the general population [6]. Losartan may circumvent unwanted side effects normally associated with angiotensin converting enzyme inhibitors(e.g. cough and angioedema) as it does not interfere with the metabolism of other peptides. (e.g. bradykinin,substance P,etc.)[7]

Angiotensin converting enzyme inhibitor Enalapril, inhibits the angiotensin II mediated vasoconstriction and aldosterone secretion. Enalapril enhance bradykinin accumulation and secondarily stimulate nitric oxide and prostaglandins.Enalapril has an established efficacy as an antihypertensive agent both as monotherapy or in combination with a diuretic[8].

Beta blockers have been widely used in the treatment of hypertension. Atenolol is beta adrenergic blocking agent that has shown to be effective given once daily as monotherapy in treatment of hypertension [9].

Amlodipine a long acting dihydropyridine calcium antagonist can be used in hypertensive patients associated with diabetes mellitus, hyperlipidemia, coronary artery disease, peripheral vascular disease, asthma, gout andis safe in patients with heart disease [10].

Amlodipine, atenolol and enalapril are commonly prescribed antihypertensive agents,they have been shown to reduce morbidity and mortality in long term clinical trials. Therefore we undertook the study to compare the efficacy and tolerability of amlodipine, atenolol, enalapril and losartan.

2. AIMS AND OBJECTIVES

To evaluate and compare the efficacy and tolerability of amlodipine, atenolol, enalapril and losartan in patients with mild to moderate hypertension.

3. METHODS

3.1. Patients: Patients aged between 30-65 years, newlydiagnosedmild to moderate hypertensive (systolic BP 140-179mm Hg, diastolic BP 90-109mm Hg)were enrolled in the study.

Patients on other antihypertensive therapy and with history of acute myocardial infarction, congestive cardiac failure, cerebrovascular accident 6 months prior to the trial, patients with liver or renal disease, diabetes mellitus, bronchial asthma, pregnant and lactating women and those taking concomitant drug therapy with drugs that raise blood pressure or intake of medications that may interfere with interpretation of results were excluded from the study.If there was lack of compliance with protocol and the patients who missed follow up visit were withdrawn from the study.

Written informed consent was obtained and the study approved by institutional ethics committee.

3.2 Study design: This was a prospective, randomized, open labelled, controlled clinical trial conducted in Hypertension clinic of tertiary care teaching hospital. Total 154 patients wereenrolled into the study as per inclusion criteria.

Pre-treatment evaluation of all patients was done. Detailed clinical history, physical examination, routinebiochemical laboratory investigations were done.Eligible patients were randomized to receive Amlodipine (2.5/5 mg/day), Atenolol (25/50 mg /day), Enalapril (5/10 mg/day) andLosartan (25/50 mg/day).

3.3Study assessment and efficacy end point:

Study treatment was started on the day of randomization. After randomization, follow up visits were scheduled at 2 weeks intervaland continued for 12 weeks. At each visit systolic blood pressure (SBP),diastolicbloodpressure(DBP)and heart rate(HR) was recorded,physical and clinical examination was done. Routine biochemical laboratory investigations were carried out at the time of enrolment and at final assessment.

The primary efficacy end point was reduction in mean systolic anddiastolic blood pressurefrom baseline to final assessment.

Target blood pressure was ≤140/90mm Hg. Those patients who did not show the desired antihypertensive effects within the stipulated time interval of4 weeks were labelled as non-responders and referred to the physician for further treatment.

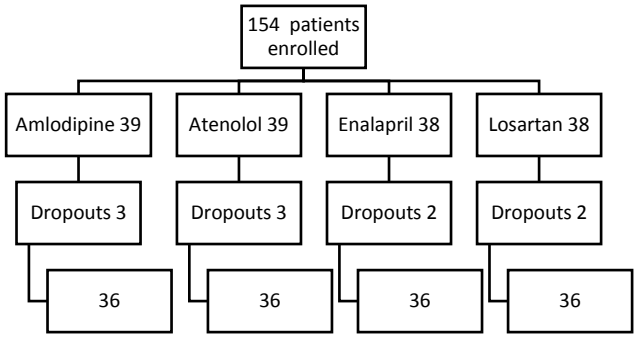
Safety outcomes included systemic adverse events and changes in various parameters observed at the time of clinical examination and biochemical investigations.

3.4. Statistics: Quantitative data within group before and after treatment was analyzed using Z test for difference between means. Quantitative data among groups was analyzed using Link Wallace test. Data on adverse effects was analyzed using z test of difference between proportions. P< or = 0.05 was taken as significant, P < 0.001 was taken as highly significant, P > 0.05 was considered insignificant.

4. RESULTS

Total 154 patients were enrolled, 39 each in amlodipine and atenolol groups and 38 each in enalapril and losartan groups. During the study period there were 3 dropouts each in Amlodipine and atenolol and 2 dropouts each in enalapril and losartan study group. As a result total 36 patients each in 4 groups were taken for statistical analysis(Fig 1)

Figure 1:Study profile



Baseline demographic characteristics which includes age, sex, weight were comparable in all study groups, there was no statistically significant difference between 4 study groups (p>0.05) (Table 1).

Table No.1:- Demography of Patients:

Parameters		Amlodipine	Atenolol	Enalapril	Losartan
		N= 39	N= 39	N= 39	N= 38
Age(yrs)		52.38± 8.54	50.08± 9.1	55.27 ± 8.49	53.32 ± 7.96
Weight(kg)		60.83 ± 8.37	60.22± 6.21	60.88 ± 6.74	60.05 ± 6.90
Sex	Male	22(56.41 %)	22(53.84 %)	22(57.89 %)	21(55.26 %)
	Female	17(43.58 %)	18(46.15 %)	16(42.10 %)	17(44.73 %)

Baseline clinical characteristics which includes mean systolic B.P., mean diastolic B.P. and heart rate was comparable, there was no statistically significant difference between 4 study groups (p>0.05) (Table 2).

Table No.2:- Baseline clinical characteristics of patients:

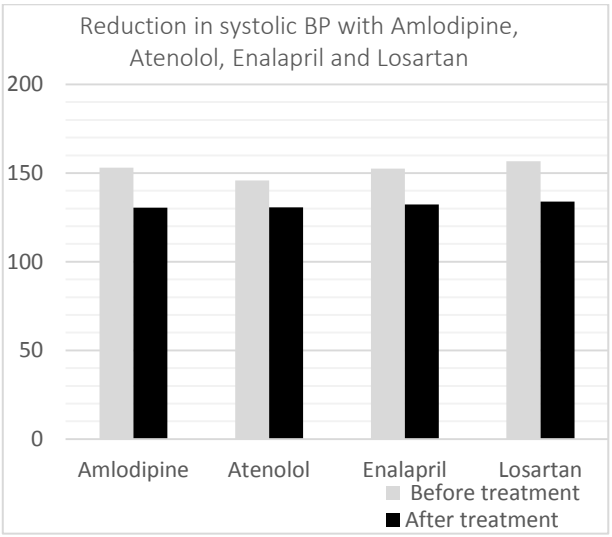
	Parameters	Amlodipine	Atenolol	Enalapril	Losartan
		N= 36	N= 36	N= 36	N= 36
1	Mean SBP in mm Hg	153± 8.62	154.66 ± 7.81	152.54 ± 7.38	156.61 ± 9.66
2	Mean DBP in mm Hg	97.44± 4.52	96± 3.85	96.94± 5.09	99.05 ± 4.34
3	Heart rate per minute	84.22± 5.71	83.27± 5.72	84± 6.17	82.33 ± 7.15

SBP- Systolic blood pressure, DBP- Diastolic blood pressure

After 12 weeks of treatment the reduction in systolic blood pressure in amlodipine, atenolol,enalapril, and losartan were 22.55±7.74, 21±7.94, 20.35±5.48, 22.61±8.41 respectively.There was no significant difference in the reduction of SBP in all 4 study drugs (p>0.05)(Table 3).

Table No.3:- Effect of Amlodipine, Atenolol, Enalapril and Losartan on systolic blood pressure:

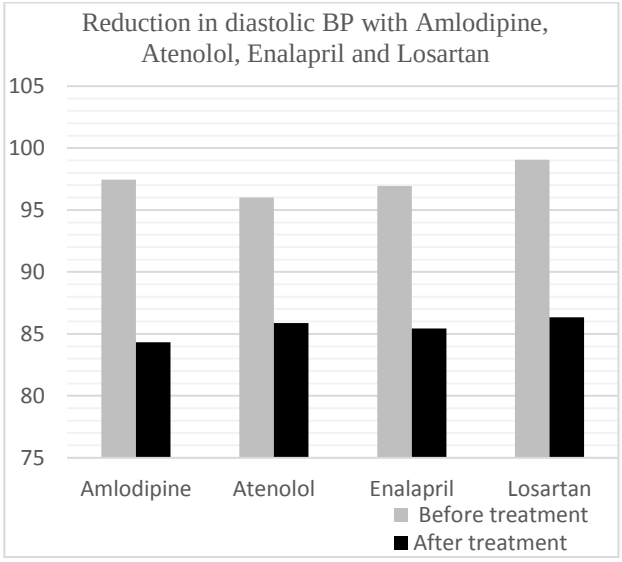
Sr. No	Parameters	Reduction in systolic BP			
		Amlodipine	Atenolol	Enalapril	Losartan
1	After 2 weeks	6.5 ± 4.66	8.83± 6.07	7.27± 3.40	9.66± 4.95
2	After 4 weeks	17.05±6.56	18.66 ± 5.36	19.5± 5.14	22.55± 6.51
3	After 8 weeks	22.11±7.26	21.66 ± 7.81	20.61± 5.55	22± 3.57
4	After 12 weeks	22.55± 7.74	21± 7.94	20.35± 5.48	22.61± 8.41



At the final assessment of study trial the reduction in diastolic blood pressure in amlodipine, atenolol, enalapril and losartan was 13.11±4.31, 10.11±3.24, 11.5±3.39, 12.72±3.38 respectively. There was no significant difference in the reduction in diastolic blood pressure in 4 study groups (p>0.05) (Table 4).

Table No.4:- Effect of Amlodipine, Atenolol, Enalapril and Losartan on diastolic blood pressure:

Sr. no	Parameters	Reduction in diastolic BP			
		Amlodipine	Atenolol	Enalapril	Losartan
1	After 2 weeks	3.72± 3.64	4.33± 3.39	4.38± 2.12	5.88± 3.51
2	After 4 weeks	10.94± 4.36	8.94± 2.63	9.83± 3.71	11.27± 3.78
3	After 8 weeks	12.83± 4.23	9.77± 3.44	11.66± 3.59	12± 3.91
4	After 12 weeks	13.11± 4.31	10.11 ± 3.24	11.5 ± 3.39	12.72 ± 3.38



In amlodipine, enalapril and losartan there was no statistically significant change in heart rate (p>0.05). But there was statistically significant reduction in heart rate in Atenolol (p<0.001) (Table 5).

Table No.5:- Effect of Amlodipine, Atenolol, Enalapril and Losartan on heart rate

Sr. No.	Parameters	Amlodipine	Atenolol	Enalapril	Losartan
1	Before treatment in beats/min	84.22± 5.71	83.27 ± 5.72	84± 6.17	82.33 ± 7.15
2	After treatment in beats/min	85.56± 5.81	69.05 ± 7.68	85.72 ± 5.47	83.5± 7.54
3	P value	P >0.05	P<0.001	P >0.05	P>0.05

In amlodipine, atenolol and losartan there was no statistically significant changes in serum potassium levels (p>0.05). But there was statistically significant increase in potassium level in enalapril(p<0.05) (Table 6).

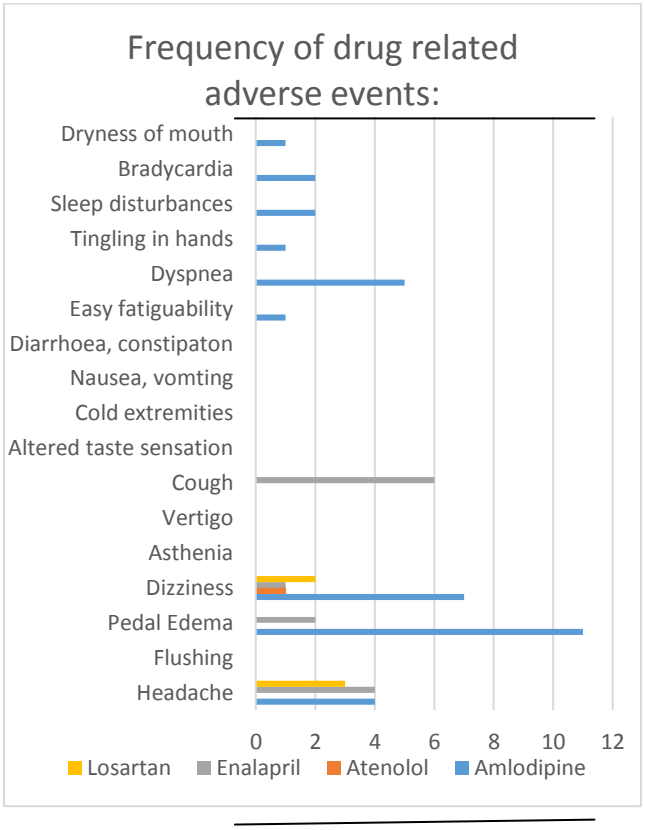
Table No.6:- Effect of Amlodipine, Atenolol, Enalapril and Losartan on serum potassium

Sr. N.	Parameters	Amlodipine	Atenolol	Enalapril	Losartan
1	Before treatment in beats/min	3.81± 0.39	3.79± 0.33	3.72± 0.35	3.74 ± 0.40
2	After treatment in beats/min	3.79± 0.36	3.69± 0.22	4.08± 0.38	3.81 ± 0.27
3	P value	P >0.05	P>0.05	P< 0.001	P>0.05

The percentage of patients suffering from adverse events was 38.88 percent, 36.11 percent, 36.11 percent and 13.88 percent in all 4 study drugs respectively.There was significant difference in the proportion of adverse events in losartan with amlodipine (p=0.009), losartan with atenolol (p=0.05)and losartan with enalapril(p=0.05). The percentage of patients with adverse events was least in the losartan group showing better tolerability profile of losartan.There was no significant difference in the proportion of adverse events in amlodipine and atenolol, amlodipine and enalapril, atenolol and enalapril groups (Table 7).

Table No.7:- Frequency of drug related adverse events:

Sr. No.	Parameters	Amlodipine	Atenolol	Enalapril	Losartan
1	Headache	4		4	3
2	Flushing				
3	Pedal Edema	11		2	
4	Dizziness	7	1	1	2
5	Asthenia				
6	Vertigo				
7	Cough			6	
8	Altered taste sensation				
9	Cold extremities				
10	Nausea, vomiting				
11	Diarrhoea, constipation				
12	Easy fatiguability	1			
13	Dyspnea	5			
14	Tingling in hands	1			
15	Sleep disturbances	2			
16	Bradycardia	2			
17	Dryness of mouth	1			



There was no significant changes observed in various biochemical parameters like Hemoglobin, Total leukocyte count (TLC), blood sugar level (BSL), serum glutamic pyruvic transaminase (SGPT), Sr. creatinine, Sr. Sodium (P>0.05) (Table 8).

Table 8: Biochemical parameters

Sr. No	Parameter	Amlodipine (n=36)		Atenolol (n=36)		Enalapril (n=36)		Losartan (n=36)	
		BT	AT	BT	AT	BT	AT	BT	AT
1	Hemoglobin	11.40± 1.07	11.58±1.46	11.53±1.10	11,55±1.16	11.44±1.00	11.17±1.16	11.17±1.17	11.16±1.14
2	TLC	7.29± 1.48	7.52±1.22	7.39±1.79	7.33±1.73	6.93±1.09	7.27±1.46	7.11±1.25	7.35±1.57
3	BSL	86.11±11.14	89.11±12.11	83.33±14.02	82.33±12.58	85±12.95	89.26±15.49	81.78±13.87	80.10±12.77
4	Sr. creatinine	0.8±0.15	0.84±0.13	0.78±0.15	0.82±0.13	0.77±0.12	0.80±0.15	0.78±0.73	0.82±0.14
5	SGPT	20.88±4.34	21.25±3.39	20.36±3.86	21.25±4.12	22.36±11.42	22.47±12.39	20.59±3.73	21.02±4.23
6	Sr. Sodium	138.25±2.98	137.83±1.10	136.61±2.65	137.44±3.40	137.16±1.84	137.11±2.71	139.64±3.07	138.83±3.37
	P value	P>0.05		P>0.05		P>0.05		P>0.05	

BT-Before treatment, AT- After treatment.

5. DISCUSSION

In the present prospective, randomized, open label study the effect of Amlodipine,Atenolol, enalapril and losartan was compared in mild to moderate hypertensive patients. When comparison of the antihypertensive efficacy of amlodipine, atenolol, enalapril and losartan was done it was found that all four drugs seem to be equally effective in reducing systolic and diastolic blood pressure after 12 weeks treatment.There was no statistical significant difference in the reduction insystolic and diastolic blood pressure in 4 study drugs.

In a prospective and randomized study in which the efficacy & tolerability of losartan was compared to amlodipine and lisinopril in mild to moderate hypertension it was found that losartan had the same antihypertensive effect as the other two drugs [11].

This was similar to our study in which losartan was comparable to amlodipine.

Philips RA et al in which amlodipine 5 /10 mg/ day & losartan 50mg / day, 12.5mg hydrochlorthiazide added to losartan after 6 weeks (if blood pressure was not controlled) in mild to moderate hypertension patients. There were greater reductions in most blood pressure measurement following treatment with amlodipine in comparisonwithlosartan with or without hydrochlorthiazide[12]. In the study of Wilson TW et al, losartan was found to be less efficacious than amlodipine or combination of losartan and hydrochlorthiazide. The findings of above two studies were not matching with our study findings.

Daholf B et al concluded that losartan and atenolol caused similar reductions in sitting diastolic blood pressure at weeks 6 & 12 in mild to moderate hypertension. This finding was similar to our study.

The above findings were confirmed in patients with isolated systolic hypertension patients receiving 50mg losartan or 50mg atenolol once daily for 16 weeks. At 8 and 12 weeks patients not controlled were given additional treatment of 12.5mg hydrochlorthiazide once daily. The study concluded that both atenolol and losartan produced comparable reductions in sitting systolic blood pressure [13].

In comparison of losartan with enalapril,Tikkanen I et al found that both reduced blood pressure to a similar extent at weeks 6 &12. This confirmed our findings [14].

Thus it could be concluded that the antihypertensive efficacy of amlodipine, atenolol, enalapriland losartan was equivalent.

Losartan did not produce any change in heart rate ($p>0.05$) after treatment. However atenolol produced statistically highly significant reduction in heart rate from 83.2 7±5.72 to 69.05 ± 7.68 per minute ($P<0.001$) (due to beta 1 blockade) This finding was similar to the finding of Dahlof B et al in which no pulse rate reduction was observed in the losartan group whereas atenolol produced a reduction in pulse rate from baseline averaging 10 beats/minute. No changes in heart rate were observed with amlodipine and enalapril therapy in our study ($P>0.05$). This may represent an advantage of losartan over atenolol because changes in heart rate which are too drastic may have adverse effects on patient's compliance particularly during the initial period of treatment.

Serum potassium levels in the losartan group were not changed to a significant extent ($P>0.05$). However in the enalapril group there was a statistically highly significant rise ($P<0.001$) from 3.72±0.35 to 4.08±0.38. This was similar to the study of the Canadian EnalaprilStudy Group (1987) in which 10/40mg ofenalapril was compared with 50/10mg of atenolol once daily in mild to moderate hypertension. It showed a statistically significant increase in the serum potassium levels after enalapril therapy. This findings are consistent with the known action of the angiotensin converting enzyme inhibitors (The Canadian Enalapril Study Group 1987) This finding may again favour losartan over enalapril as clinically significant hyperkalemia may cause arrythmias or even convulsion.

Five patients (13.88%) in the losartan group reported headache and dizziness as adverse effects. This finding was similar to the finding of Gradman A.H et al in which headache (10-20% incidence) was the most common adverse experience in the losartan treated groups. A significantly lower proportion experienced nausea in the losartan 50mg and 150mg groups. Upper respiratory tract infection and nasal congestion were also reported but did not appear to be dose related .Cough was reported in 3% of losartan 50 mg group [15].

In the study of Dahlof B et al headache was the most commonly reported adverse experience with 16% incidence in the losartan group. Reasons for discontinuing therapy in the losartan group were dizziness (1) and abdominal pain (1) [9].

55.4% patients experienced at least one adverse event in the losartan treated group as found by Phillips RA et al. There was no individual treatment related adverse event that occurred with an incidence of more than 3% in the losartan group [12]. The incidence of dry cough was 1% as a spontaneously reported discomfort and 3% as clinical adverse experience in the losartan group as reported by Tikkanen I et al. [14].

In the amlodipine group, 14 patients (38.88%) presented with adverse effects. Pedal edema was the commonest complaint. Other adverse effects reported were dizziness, headache and sleep disturbances. Wilson TW et al found that edema was a complaint of 25% of the subjects in amlodipine group substantially higher than 2% in the group receiving losartan, and losartan with hydrochlorthiazide[10].

57.8% patients experienced at least 1 adverse event in the amlodipine group in the study of Phillips RA et al. The most frequent treatment related adverse event (>3%) was peripheral edema with most cases rated as mild. [12] However in the study of Verma U et al no incidence of edema or fluid retention was found.

13 patients (36.11%) in the atenolol group were observed to have adverse effects. The most frequently occurring was dyspnoea followed by sleep disturbances, bradycardia, dizziness, easy fatigability and tingling in hands. Dahlof B et al reported at least 1 adverse experience in 57% of patients in the atenolol group. Headache was the most commonly reported adverse experience with 19% incidence in the atenolol group. Nausea (6%) and sweating (4%) was more common in the atenolol group. Reasons for discontinuing therapy were dizziness(1), abdominal pain(1), bradycardia(1), atrial fibrillation (1), sweating, asthenia or fatigue(1), headache, cold extremities, joint swelling and rash (1) [9].

The frequency of dyspnoea was 0.6% as told by the patients and 6% as elicited by the investigator from controlled studies in hypertensive patients.

36.11% of patients (13 patients) reported adverse effects with enalapril. Dry cough was the commonest complaint .Other complaints were headache, pedal edema and dizziness. Gradman AH et al recorded cough as an adverse experience in 8% of enalapril treated patients compared with 3% in the placebo group [15].

The incidence of dry cough was 12.2% as a spontaneously reported discomfort and 15.1% as a clinical adverse experience in the enalapril group[14].

Wu SC et al found that losartan has superior tolerability to amlodipine. This finding was comparable to our study findings[11].

Gradman AH et al reported that losartan was well tolerated as evidenced by clinical laboratory safety profiles that were comparable to those observed with enalapril maleate [15].

Thus we can conclude that for the same antihypertensive effect, losartan was better tolerated than amlodipine, atenolol and enalapril.

6. CONCLUSION

We evaluated and compared the effects of amlodipine, atenolol, enalapril and losartan in patients with mild to moderate hypertension in terms of efficacy and tolerability. We found that all the four drugs are equal efficacious as antihypertensive agents. When the adverse effect profile was compared, losartan was observed to be better tolerated than amlodipine, atenolol and enalapril. Losartan did not have any effect on heart rate or serum potassium. Thus for the same antihypertensive effect, losartan was found to be comparatively safer than amlodipine, atenolol and enalapril in patients with mild to moderate hypertension.

To evaluate the effect of losartan on morbidity and mortality long term studies are required. Due consideration should be given to its future use as a first line antihypertensive agent.

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