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Original Research Article

Reno-protective effect of angiotensin converting enzyme inhibitor and angiotensin II receptor blockers in type 2 diabetic nephropathy with elevated urine albumin to creatinine ratio

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ABSTRACT

Background: Nephropathy is responsible for an End Stage Renal Disease (ESRD) in type 2 diabetics if uncontrolled. The monotherapy/combination of Angiotensin Converting Enzyme inhibitor (ACEi) and Angiotensin II Receptor Blockers (ARBs) can retard the progression of urine albumin to creatinine ratio in diabetic nephropathy but, the data shows an inconsistency in the efficacy of these drugs. So, the present study was aimed at comparing the reno-protective effect of ACEi/ARBs in type 2 diabetics.
Methods: A prospective, randomized study is conducted at Maharaja's Institute of Medical Sciences, Nellimarla, Vizianagaram, Andhra Pradesh, India with 100 patients, who are randomly categorised and equally distributed among the two groups and treated with Enalapril (ACEi) and Losartan (ARBs) for 6 months. 24-hour urine albumin to creatinine ratio and HbA1c are recorded before and after the treatment.
Results: Enalapril and losartan showed a non-significant reduction in urine albumin to creatinine ratio from 196.2±17.5 to 185.9±15.2 (p=0.66) and 236.8±16.3 to 193.7±20.6 (p=0.11) respectively. A strict glycemic control has shown a reduction in HbA1c in both the groups.
Conclusions: Present findings suggested that losartan is relatively more effective than enalapril in reducing the 24-hour urine albumin to creatinine ratio of diabetic nephropathy patients. Along with these drugs, regulation of blood glucose will assist in retarding the progression of nephropathy in type 2 diabetics.

Keywords: Angiotensin converting enzyme inhibitor, Angiotensin II receptor blockers, Diabetic nephropathy, End stage renal disease

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder, relentlessly increasing economic burden on the society.[1] According to World Health Organization (WHO) around 400 million adults are diabetic across the globe and the number would be doubled by 2030. Global diabetes prevalence is similar in men and women, but it is slightly higher in men <60 years of age and in women at older ages.[2] Diabetic nephropathy (DN) is a clinical syndrome characterized by elevated urine albumin to creatinine ration (>30 mg/gm), increased blood pressure, a decline

in glomerular filtration rate (GFR).[3] DN is one of the common complications affecting one third of people with type 2 DM and the incidence is increasing by 10% every year. Chronic Kidney Disease (CKD) in type 2 diabetics is markedly increasing incidence of cardiovascular risk. Screening for DN must be initiated at the time of diagnosis in patients with type 2 diabetes. Since, around 7% of them already have microalbuminuria at that time, if microalbuminuria is absent, the screening must be repeated annually.[4] Early detection and treatment of DN will reduce the progression of renal disease characterized by early renal inflammation, followed by subsequent tubulointerstitial fibrosis, tubular atrophy, glomerulosclerosis and End Stage Renal Disease (ESRD).[5,6] Intensive glucose and blood pressure control reduces urine albumin to creatinine ratio, slows renal dysfunction and protects against microvascular complications.[7]

It is mandatory to develop strategies to prevent the progression of renal disease or even to restore renal function by inducing regression. The use of either Angiotensin Converting Enzyme inhibitor (ACEi)/ Angiotensin II Receptor Blockers (ARBs) is recommended as a first line of therapy for diabetic patients with microalbuminuria, even if they are normotensive. Ramipril has decreased the risk of nephropathy by 24% and the risk of cardiovascular death in patients with type 2 diabetes by 37%.[8,9] Trails conducted with ARBs on type 2 diabetic nephropathy patients have shown a reno-protective effect by slowing the progression of nephropathy.[10] Both the ACEi and ARBs might provide the renoprotection by decreasing the systemic blood pressure, intra glomerular pressure and proteinuria. But the current data shows inconsistent results on the efficacy of ACEi and ARBs.[11,12] The combination therapy of ACEi and ARBs is not recommended as it does not provide any additional benefits as compared to monotherapy and may even increase the risk of hyperkalemia.[13] So, the present study was taken up to check the reno-protective effect of enalapril (ACEi) and losartan (ARBs) monotherapy in controlling the progression of nephropathy in type 2 diabetics with urine albumin to creatinine ratio (30-300 mg/g).

METHODS

Present study was prospective and randomized, conducted at Maharajah's Institute of Medical Sciences, Nellimarla, Andhra Pradesh, India during the period January 2018 to January 2019, among the people attending the OP and IP departments. Informed consent in local language was taken from the patients. IEC clearance was obtained.

Hundred subjects of type 2 diabetics with urine albumin to creatinine ratio >30 mg/gm are selected. They were randomly categorized and equally distributed among the two exposure groups and treated with a fixed dose of enalapril and losartan for 6 months duration.

Inclusion criteria

Patients diagnosed as type 2 diabetes with urine albumin to creatinine ratio >30 mg/gm were included.

Exclusion criteria

Patients with coronary artery diseases, systemic infections and non-diabetic renal disease were excluded from the study.

Procedure

The selected patients are treated with enalapril and losartan with a fixed dose for a period of 6 months. The following data was collected from both the groups before and after the treatment.

Baseline data includes name, age, sex, occupation, weight, height, personal history, family history and drug history. Other investigations include FBS, PPBS, HbA1c, lipid profile and 24-hour urine for albumin and creatinine estimation.[14,15] While collecting the urine sample, UTI infection to be checked.

Statistical analysis

P values <0.05 are considered significant. All the values are calculated as mean±SD. Student 't' test and Two-way Anova test are used to find the statistical significance. SPSS software was used for data analysis.

RESULTS

The study was conducted at Maharaja's Institute of Medical Sciences, Nellimarla, Andhra Pradesh, India with 100 patients diagnosed as type 2 diabetic with urine albumin to creatinine ration >30 mg/gm, who were randomly allocated to two exposure groups and treated with enalapril and losartan monotherapy for 6 months duration. The 24-hour urine albumin to creatinine ratio (mg/gm), HbA1c was recorded before and after the treatment and the results are tabulated.

Table 1 shows the comparison of enalapril (angiotensin converting enzyme inhibitor) and losartan (angiotensin II receptor blocker) in type 2 diabetic with 24-hour urine albumin to creatinine ratio (mg/gm). The urine albumin to creatinine ratio has reduced from 196.2±17.5 to 185.9±15.2 when treated with enalapril and 236.8±16.3 to 193.7 + 20.6 with losartan. A better reduction in albumin to creatinine ratio was observed with losartan as compared to enalapril. The reduction was more in females from 251.4±18.8 to 180.0±27.5 compared to males from 222.2±22.2 to 207.4±32.4 with losartan (Table 1).

Table 1: 24-hours urine albumin to creatinine ratio (mg/gm).

Drug		Before			After			P value
		Male	Female	Total	Male	Female	Total	
Enalapril	N	33	17	50	33	17	50	0.66
	Mean	214.8	177.6	196.2	193.2	178.6	185.9	
	SD	22.8	26.1	17.5	24.2	20.8	15.2	
Losartan	N	28	22	50	28	22	50	0.11
	Mean	222.2	251.4	236.8	207.4	180.0	193.7	
	SD	27.2	18.8	16.3	32.4	27.5	20.6	

Table 2: HbA1c in both the groups.

Drug		Before			After			P value
		Male	Female	Total	Male	Female	Total	
Enalapril	N	33	17	50	33	17	50	0.57
	Mean	7.66	7.48	7.60	7.34	7.02	7.18	
	SD	0.78	0.75	0.48	0.78	0.64	0.49	
Losartan	N	28	22	50	28	22	50	0.31
	Mean	7.96	8.42	8.19	7.68	7.32	7.50	
	SD	0.45	0.61	0.36	0.72	0.93	0.55	

Table 3: Urine albumin to creatinine ratio and HbA1c in both the groups.

Parameter		Enalapril		Losartan		P value
		Mean	SD	Mean	SD	
Albumin/creatinine ratio	Before	196.2	17.5	236.8	16.3	1.07
	After	185.9	15.2	193.7	20.6	0.76
HbA1c	Before	7.60	0.48	8.19	0.36	0.32
	After	7.18	0.49	7.50	0.55	0.67

Figure 1 shows a better and non-significant reduction in urine albumin to creatinine ratio with losartan (p=0.11) as compared to enalapril (p=0.66) (Figure 1). HbA1c levels were determined in both the exposure groups and tabulated in Table 2.

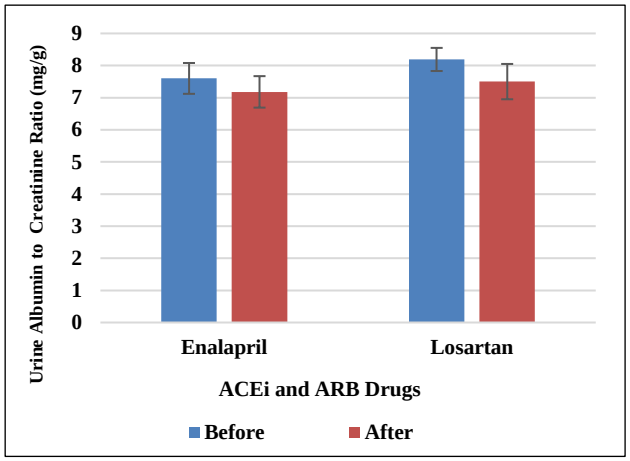

Figure 1: 24-hours urine albumin to creatinine ratio before and after the treatment with enalapril and losartan.

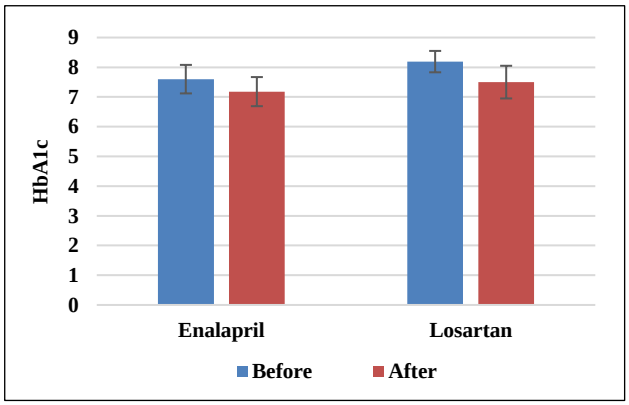

Figure 2: HbA1c levels in both the groups before and after glycemic control.

A strict glycemic control was instructed through the treatment duration and glycemic index was ascertained with HbA1c levels. There was a reduction in HbA1c levels from 7.60±0.48 to 7.18±0.49 in enalapril group and 8.19±0.36 to 7.5±0.55 in losartan group (Table 2). Figure 2 shows a non-significant reduction in of HbA1c levels in both enalapril (p=0.57) and losartan group (p=0.31) after a strict glycemic control for 6 months (Figure 2).

The correlation of urine albumin to creatinine ratio and HbA1c levels between the two groups are shown in Table 3. There was no significant difference in 24-hour urine albumin to creatinine ratio between enalapril and losartan before (p=1.07) and after (p=0.76) the treatment. Even the HbA1c levels were not significantly differing between enalapril and losartan before (p=0.32) and after (p=0.67) the treatment (Table 3).

DISCUSSION

A decrease in GFR in diabetic nephropathy via glomerular hypertension leads to increased glomerular permeability, albuminuria and renal damage. Hsu FY et al, study observed a significant reduction in urine microalbumin levels in diabetic nephropathy patients treated with ACEi as compared to ARBs.[16]

Wang K et al, demonstrated a significant reno-protective effect of ARBs over ACEi in reducing the microalbuminuria which is similar to this study, where a reduction in progression of urine albumin to creatinine ratio is observed in diabetic nephropathy patients treated with losartan when compared to enalapril.[12] If we observe the mechanism of action ACEi act by blocking the enzyme ACE, opposing the conversion of angiotensin I to angiotensin II, thereby decreasing the renal damage. Though, ACEi block formation of angiotensin II, it is significantly produced in the peripheral tissues through an ACE-independent conversion. Chymase a secretory serine protease inhibitor is acting as an ACE convert angiotensin I to angiotensin II.[17] In the presence of ACEi a significant elevation of chymase expression and activity might be responsible for elevation of angiotensin II levels. This is not the case with ARBs, which oppose the action of by blocking the binding of angiotensin II to their receptors. This might be one of the reasons as why ARBs are more effective than ACEi in controlling the progression of nephropathy in type 2 diabetics. The inconsistency might be even because of not including all the drugs of these groups and a small sample size.

In this study, author observed a strict glycemic control had a non-significant reduction in the progression of nephropathy in both the groups which is accordance with Vivian E et al study.[18]

From the findings of the present study, it may be concluded that losartan is more effective as compared to enalapril in controlling the of 24-hour urine albumin to creatinine ratio and the progression of diabetic nephropathy. A reduction in HbA1c levels in both the groups with the regulation of blood glucose also assist in the reducing the progression of diabetic nephropathy.

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