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A Patient Outcome Study in Type 2 Diabetic Patients with Hypertension with the Treatment of Angiotensin-Converting Enzyme Inhibitors versus Angiotensin Receptor Blockers for Control of Microalbuminuria

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Abstract: *Angiotensin convertase enzyme inhibitors(ACEi) or angiotensin receptor blockers(ARBs) in patients with diabetes mellitus(DM) and hypertension decreases urinary albumin excretion rate(UAER). Studies on head to head comparison of ACEi and ARBs with reduction of proteinuria as a primary outcome in the above mentioned patients are limited. This study was done to compare the efficacy of losartan and enalapril in controlling moderately increased albuminuria in hypertensive type 2 DM Indian population.*

Methods: *This was a single centre, prospective, randomized, open label, active controlled study carried out on patients with well controlled type 2 DM with hypertension and UAER of 20200µg/ min. Patients were recruited from January 2013 to December 2014 and followed for 24 weeks. Sixty patients were recruited and randomized to receive enalapril(n=30, group A) or losartan(n=30, group B). Enalapril and losartan were started at 5 and 50 mg/d respectively and uptitrated every 2 weeks to the maximum of 20 mg enalapril and 100 mg losartan. Patients with blood pressure of >150/95 mm of Hg at the end of 8 weeks, were started on other antihypertensive drugs. Albumin excretion rate was calculated in a 24 hr sample using enzyme immunoassay.*

Results*: Baseline characteristics were equally matched in both groups. The mean age at presentation was 56±11.2 and 54.10.8 years in group A and B respectively. All had hypertension with mean SBP and DBP in group A were 167.73±10.58 and 99.20±4.16 and in group B were 159.13±10.49 and 100.33±6.33 respectively. Mean UAER in group A was 133.33±45.79 and in group B was 117.80±34.0. After 24 weeks of follow up, both drugs were succeeded in controlling hypertension and albuminuria significantly.*

Conclusions: *In patients with type 2 diabetes mellitus and hypertension, treatment with ACEi or ARBs is equally effective in reducing blood pressure and albuminuria.*

I. Introduction:

The diabetes epidemic continues to grow unabated, with a staggering toll in micro- and macrovascular complications, disability, and death. Hypertension in diabetic patients is 1.5 to 2 times more frequent than non-diabetic individuals[1.] The prevalence of hypertension in those with type 2 diabetes was: 71%, 90%, and 93% in the normoalbuminuria, microalbuminuria, and macroalbuminuric group, respectively[2,3]. Patients with diabetic nephropathy and hypertension have progressive decline in renal function and the treatment of hypertension in these patients slows the rate of loss of renal function[4,5] . The renin-angiotensin system (RAS) has been implicated in the pathophysiology of hypertension, cardiovascular disease including ventricular hypertrophy, remodelling, end organ damage, heart failure, more recently atherosclerosis and renal failure. RAS blockade with either ACE inhibitors(ACEi) or Angiotensin Receptor Blockers (ARBs) results in prevention of microalbuminuria[6] and decrease in the rate of progression to more advanced stages of diabetic nephropathy[7,8]. In MICRO-HOPE (sub study of HOPE study) analysis, ramipril reduced the rate of overt nephropathy by 24%.[7] RENAAL study, a double blind randomized control study has shown that the use of losartan in type 2 DM with advance renal disease resulted in 28% reduction in ESRD(p-0.002) and 35% reduction in level of proteinuria($p<0.001$)[8]. RAS blocade also results in reduction in protenuria independent of blood pressure control[9].To our knowledge studies on head to head comparison of ACEi and ARBs with reduction of proteinuria as a primary outcome in hypertensive type2 DM patients are limited[10] . This study was done to compare the efficacy of losartan and enalapril in controlling moderately increased albuminuria in hypertensive type 2 DM Indian population.

II. Material And Methods

This was a randomised open label study carried out in patients with type 2 Diabetes mellitus with hypertension attending the medicine outpatient department of King George Hospital, Visakhapatnam. Patients were recruited from January 2013 to December 2014 and followed for 24 weeks. A synopsis regarding the

present study was submitted to the Institutional Ethics Committee and the permission was taken before starting the study.

III. Methodology

Sixty patients were recruited and randomly categorised into two groups(group A =30, group B=30). At the commencement of trial the patients were subjected to thorough clinical examination and necessary investigations and baseline values were recorded. At the initiation of the study all antihypertensives were stopped and group A and group B patients were started on 5 mg of EnaIapril and 50 mg of losartan respectively. Patients were followed every 2 weekely for 12 weeks and then every monthly till the end of the follow up. By the end of 8th week, drug doses were titrated to the maximum of 20 mg for enalapril and 100 mg for losartan. Patients with blood pressure of >150/95 mm of hg at the end of 8 weeks, were started on other antihypertensive drugs which include calcium channel blockers and diuretics. At the end of 12 weeks, patients with blood pressure>150/95 mm of hg were eliminated from the study. Before the study was started the status of glycemic control was assessed in the patients. The patients were included in the study only after glycemic control was achieved (Glycated haemoglobin <9.0, Plasma Glucose: -Fasting<126 mg/d, 2 hour post prandial<200 mg/dl) and through the study the glycemic control was maintained.

Blood Pressure Measurement: Blood pressure was measured with a standard mercury sphygmomanometer with patients lying down. The cuff was applied to arm after which pressure was recorded two times at 5 minutes intervals, while the patient remained at rest. The mean of two readings were recorded. Blood pressure was targeted to ≤ 140/90 mm of Hg.

Urinary Albumin Estimation- Quantitative estimation of urinary albumin was done with the 24 hrs urine sample. Albumin in urine was measured by using Enzyme Immunoassay for quantitative determination of human albumin in urine (EIA Test). Each time UAER was calculated twice from 24 hours urine sample and mean of two values were calculated.

IV. Statistical Analysis

Continuous quantitative variables were expressed as mean ± standard deviation. Unpaired t-tests were used for between-group comparisons and paired t-tests were used for within group comparisons. Categorical variables were compared by the chi squared test and Fisher's exact test, as appropriate. All statistical procedures were performed using SPSS software (version 16, SPSS Inc, Chicago, IL).

V. Results

Total 150 patients were evaluated and finally 60 patients were studied and followed for 24 weeks. Baseline characteristics are shown in table 1. At the initiation of the study the baseline characteristics were equally matched in both groups. Male to female ratios in group A and B were 16:14and 15:15 respectively. Most of the patients were more than 50 years of age at presentation with mean age of 56±11.2 and 54.10.8 years in group A and B respectively. All had hypertension with mean SBP and DBP in group A were 167.73±10.58 and 99.20±4.16 and in group B were 159.13±10.49 and 100.33±6.33 respectively. All had controlled diabetes status at presentation with HbA1C of 7.41±1.1 and 7.28±0.9 in either groups respectively. Mean UAER in group A was 133.33±45.79 and in group B was 117.80±34.0.

Table 1. Base line characteristics

Variable	Group A	Group B	P
Age (years)	56±11.2	54±10.8	0.34
Duration of diabetes	9.4±1.9	8.9±1.7	0.21
FBS	118.36±12.8	119.9±11.7	0.38
PPBS	186.5±15.7	168.16±14.3	0.06
HbA1C	7.41±1.1	7.28±0.9	0.28
SBP	167.73±10.58	159.13±10.49	0.33
DBP	99.20±4.16	100.33±6.33	0.29
MAP	121.83±4.53	119.93±6.76	0.34
UAER	133.33±45.79	117.80±34.0	0.22

Table 2. effect of enalapril on hypertension and urinary albumin excretion

	Baseline		After 24 wks		t-value	p-value
	mean	SD	mean	SD		
Systolic BP	167.73	10.58	141.80	5.90	14.7213	<0.0001 (S)
Diastolic BP	99.20	4.16	85.43	3.42	14.6584	<0.0001 (S)
Mean Arterial Pressure (MAP)	121.83	4.93	104.10	3.39	20.0016	<0.0001 (S)
UAER (µg/min)	133.33	45.79	103.27	31.79	8.4168	<0.0001 (S)

Table 3. effect of losartan on hypertension and urinary albumin excretion

	Baseline		After 24 wks		t-value	p-value
	mean	SD	mean	SD		
Systolic BP	159.13	10.99	143.60	8.56	9.6516	<0.0001 (S)
Diastolic BP	100.33	6.06	86.53	4.42	9.7168	<0.0001 (S)
Mean Arterial Pressure (MAP)	119.93	6.76	105.13	5.01	15.8474	<0.0001 (S)
UAER (µg/mt)	117.80	34.00	94.53	27.58	12.5507	<0.0001 (S)

Table 4. comparision of enalapril and losartan on hypertension and urinary albumin excretion

	Group A		Group B		
	Mean	SD	mean	SD	p-value
UAER difference	30.60	19.20	22.93	10.65	0.0608
SBP	141.80	5.90	143.60	8.56	0.32
DBP	85.43	3.42	86.53	4.42	0.28

VI. Discussion

It is known that treating hypertension in patients with diabetes would result in primary and secondary prevention of diabetic nephropathy. Several RCTs compared the effect of ACEI vs other antihypertensives in reducing the incidence of microalbuminuria in type 2 diabetes with normoalbuminuria and showed that there was no significant difference between them in achieving the outcome[11,12,13]. Ravid and colleagues conducted a double-blind randomized study of 94 normotensive microalbuminuric type 2 diabetic patients who received enalapril or placebo for 5 years[14]. In the actively treated group kidney function remained stable and only 12% of the patients developed diabetic nephropathy, whereas in the group receiving placebo kidney function declined by 13% and 42% of the patients developed nephropathy. Our study included patients with hypertension and moderately increased protenuria and showed ACEi achieved significant reduction in hypertension and protenuria(P<0.0001 for SBP, DBP and UAER). Melbourn diabetic nephropathy study group had conducted a study on microalbuminuric and hypertensive diabetic population and has shown that there is no significant difference in blood pressure control and AER reduction between perindopril and nefidipine[15]. In patients with type 2 diabetes with hypertension and moderately increased albuminuria , IRMA2 study has shown that irbesartan has got antiproteinuric effect irrespective of blood pressure control[9].

In that study, 5.2% of the 300 mg group, 9.7% of the 150 mg group and 14.9% of the placebo group developed protenuria and the results were significant between high dose irbisartan and placebo group(p<0.0001). However the average blood pressure during the course of the course of the treatment was almost similar between the three groups(141/83 mm Hg in the 300mg group, 143/83 mmHg in the 150-mg group, and 144/83 mm Hg in placebo group). There are several studies which compared the effect of ACEI and ARB on blood pressure control and showed that both were equal in efficacy and untoward effects were high in ACEI group[16]. Only few studies have compared the effect of ACEI vs ARB in achieving renoprotection[17, 18]. In a retrospective study by Robles NR etal[17], 154 patients were treated with ACEI and 85 patients received ARBs. Pre-ESRD survival was 91.9% at three years, 81.6% at five years and 61.9% at seven years of follow-up for patients treated with ACE inhibitors and for patients treated with ARBs, pre-ESRD survival was 95.3% at three years, 82.1% at five years and 78.2% at seven years of follow-up and there was significant difference in patient survival favoring ARBs (p=0.02). In that study they have looked for renal survival and noted that at 36 months, the comparative odds ratio for having started renal replacement therapy or reaching end-stage renal failure was 0.246 (95% confidence interval 0.114–0.531, p<0.001) again favouring ARBs. However in this study they didn't look for the effect of drugs on reduction of protenuria and hypertension. In another prospective multicentre, double blind study by Bartnett AH etal[18], 250 subjects with type 2 diabetes and early nephropathy received either the angiotensin II–receptor blocker telmisartan (80 mg daily, n= 120 subjects) or the ACE inhibitor enalapril (20 mg daily, n=130 subjects).

It showed that telmisartan was not inferior to enalapril in terms of renoprotection(After five years, the change in the glomerular filtration rate was -17.9 ml per minute per 1.73 m^2 of body-surface area, with telmisartan, as compared with -14.9 ml per minute per 1.73 m^2 with enalapril). As a secondary end point, they also showed that there is no significant difference in reduction of proteinuria, however they didn't show the absolute value of reduction (urine albumin excretion ration of 1.03: 0.99 between telisartan and enalapril). In our study we have shown that there was no significant difference between enalapril and losartan in lowering blood pressures and UAER. The mean reduction in SBP and DBP in enalapril group was from 167.73±10.58 and 99.20±4.16 to 141.80±5.90 and 85.43 ± 3.42 respectively and in losartan group was from 159.13±10.49 and 100.33±6.33 to 143.60±8.56 and 86.53±4.42 respectively(p<0.32 and 0.28 for SBP and DBP)) and the mean

reduction in UAER for enalapril and losartan after 24 weeks were from133.33±45.79 to 117.80±34.0. and from 103.27± 31.71 to 94.53 ± 24.58 respectively (p-0.0608)). Our study results are comparable to the study conducted by Lacourcière Y etal[10], in which they have treated 92 type 2 diabetic patients with hypertension either with losartan or enalapril in combination with other drugs and followed them for 52 weeks and showed that both hypertension and UAER were significantly decreased by both losartan and enlapril with out a stastical difference between the groups. This kind of study was conducted for the first time in Indian population to our knowledge, where we have compared the effect of ACEI vs ARBs on hypertension and renoprotection. There are several limitations in this study. The study period was very short, so that we couldn't look for patient and renal survival. We have omitted other cardiovascular risk factors like smoking and dyslipidemia. However in our study there was no cardiovascular mortality and morbidity noted.

VII. Conclusion

After 24 weeks of follow up the effect of enalapril and losartan was assessed on hypertension and urinary albumin excretion (table 2 and 3). Both were succeeded in controlling hypertension significantly with mean SBP and DBP after 24 weeks of enalapril of 141.80±5.90 and 85.43 ± 3.42 respectively. and with losartan the mean were 143.60±8.56 and 86.53±4.42 for SBP and DBP. They also succeeded in controlling microalbuminuria , however there was no regression in the UAER towards normal. The mean UAER for enalapril and losartan after 24 weeks were 103.27± 31.71 and 94.53 ± 24.58 respectively. On comparision there is no significant difference between enalapril and losartan on control of hypertension and UAER (Table 4). During the follow up there were no cardiovascular morbidity or mortality noted.

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