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Comparison of Efficacy of Telmisartan and Enalapril in Patients with Diabetic Nephropathy

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Abstract: Diabetic nephropathy is the leading cause of end – stage renal disease. It is characterised by Hypertension and persistent proteinuria. If ineffectively controlled, a progressive decline in renal function can result in end – stage renal disease. The main objective of this study was to evaluate the efficacy of Telmisartan vs Enalapril on Diabetic Nephropathy in patients with type 2 diabetes. Patients included in this study were patients who had type 2 diabetes treated by diet and/or oral hypoglycaemics; Patients treated with insulin, if they were diagnosed as being diabetic at the age of > 40 years, had been in receipt of oral hypoglycaemics for > 1 year before being treated with insulin and had a body mass index of >25kg/m^2; patients who have mild to moderate hypertension (resting systolic / diastolic blood pressures < 180/95 mmHg) while receiving an ACE Inhibitor for > 3 months before entering the study. From 344 subjects with diabetic nephropathy included in the study, 328 patients were included in the final analysis. 16 patients were dropped from the study (15, 01 patients from Telmisartan and Enalapril groups respectively). At the end of the study the reduction in urine albumin was more with Enalapril (Mean difference 43.75 ± 4.003) when compared with Telmisartan (Mean difference 36.49 ± 3.23). The p values were < 0.05 for both groups and it was found that reduction of diabetic nephropathy in Enalapril treatment group at the end of the study is statistically differs than the Telmisartan treatment group. We concluded that Enalapril confers strong renal protection in patients with type 2diabetes and nephropathy. Telmisartan is not inferior to Enalapril in providing Reno protection in subjects with Type 2 Diabetes and early nephropathy. This result is consistent with emerging data that support the clinical equivalence of angiotensin II- receptor blockers and ACE inhibitors in various conditions associated with high cardiovascular risk.

Key words: Diabetic Nephropathy · End – Stage Renal Disease · Renin – Angiotensin Aldosterone System · Telmisartan · Enalapril

INTRODUCTION

Diabetes Mellitus (DM) is the most frequent cause of chronic kidney failure in both developed and developing countries [1]. Diabetic nephropathy, also known as kimmelstiel – Wilson syndrome or nodular diabetic glomerulosclerosis / intercapillary glomerulonephritis, is a clinical syndrome characterized by albuminuria (>300 mg/day or >200 mcg/min) confirmed on at least two occasions 3-6 months apart, permanent and irreversible decrease in glomerular filtration rate (GFR) and arterial hypertension [2]. The syndrome was first described by a British physician Clifford Wilson (1996-1997) and American physician Paul Kimmelsteil (1900-1970) in 1936 [3].

Diabetic nephropathy is a chronic condition developing over many years characterized by Gradual increasing urinary albumin excretion (UAE), High blood pressure, Declining GFR, Absence of other renal / renal tract disease, Presence of diabetic retinopathy.

The aim of this study was to analyse the effect of two widely used drugs Telmisartan and Enalapril on urinary albumin.

MATERIALS AND METHODS

This was a prospective observational study carried out in Sri Bhadrakali Diabetic Clinic, Kishanpura, Hanamkonda, Telangaana, India. Institutional Human Ethics committee endorsement was seek and obtained

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before conduct of the trial (VCOP/PHARMD/V/2016/10/19). Selection of subjects was done according to the following inclusion-exclusion criteria:

Inclusion criteria: Patients who had type 2 diabetes treated by diet and/or oral hypoglycaemics; Patients treated with insulin, if they were diagnosed as being diabetic at the age of > 40 years, had been in receipt of oral hypoglycaemics for > 1 year before being treated with insulin and had a body mass index of >25kg/m^2 ; patients who have mild to moderate hypertension (resting systolic / diastolic blood pressures < 180/95 mmHg) while receiving an ACE Inhibitor for > 3 months before entering the study.

Exclusion Criteria: Patients with a serum creatinine of >140ummol/L ; Patients with renal dysfunction not due to diabetes , a single kidney or known renal artery stenosis, congestive heart failure, hypersensitivity to study drugs, or a history of angioedema.

Written and oral informed consent forms were obtained and evaluated before the study procedures.

The patient disposition is given in Fig. 1.

Thus, a total of 344 subjects with diabetic nephropathy were included in the study. They were randomized in two study groups, to receive Telmisartan (Group 1), Enalapril (Group 2). Of these, 16 patients dropped from the study (15 and 01 patients from the Telmisartan and Enalapril groups respectively). The treatment was carried out with any one choice of the two options, administered once daily.

Patient's medical history and demographic details were documented at screening visit. Before starting the therapy, first parameters were evaluated from patient's records. Patients received the drugs for 3 months period and returned for final evaluation at the last day. During the course of the trial, progress of patients was tracked using the regular visits. Clinical and laboratory collected data included height, weight, systolic and diastolic blood pressure (BP), Fasting Blood Glucose (FBG), Post Prandial blood Glucose (PPG), glycated hemoglobin (HbA1C) and lipid profiles.

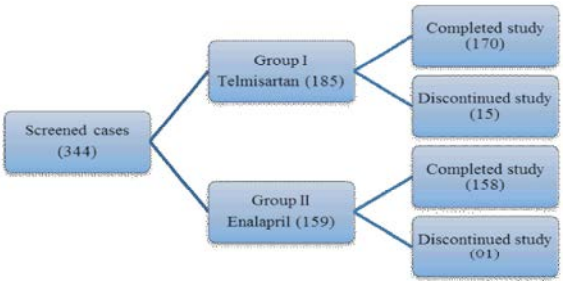

Fig. 1: Distribution of Patients.

Measurements of Treatment Efficacy: The primary efficacy measure for this study was the reduction in Urine Albumin. Subjective urinary albumin levels were assessed by laboratory test.

The secondary efficacy measures collected were systolic and diastolic blood pressure (BP), Fasting Blood Glucose (FBG), Post Prandial blood Glucose (PPG), glycated haemoglobin (HbA1C) and lipid profiles.

Statistical Analysis: Data analysis was done using Graph Pad Prism software (version 7). Mean and Standard deviation (SD) were calculated for the normal distributed variables - efficacy measures, laboratory measures and vital signs. Difference between quantitative variables was evaluated by using t-Test [unpaired]. Statistical significance was recognized at $p < 0.05$.

Data analysis was done by using Graph pad prism (version 7). Values are for Mean and Standard deviation (SD) were calculated for efficacy measures and laboratory measures. For the efficacy measures, the treatment group differences in change from baseline to endpoint were determined. Significance of difference between quantitative variables was evaluated using the T-test (unpaired). In all two groups was carried out using T-test (unpaired). Results were reported as Mean ± standard deviation (SD), Mean difference and statistical significance was recognized at p values <0.05.

RESULTS

Demographic characteristics of the study population are given in Table 1.

Clinical Characteristics: All the vital signs were measured at start and at the end of the study. Mean difference of laboratory parameters in two drugs are given in Table 2. Blood pressure (systolic & diastolic), Mean arterial pressure (MAP), pulse pressure (PP), FBS, PLBS, HbA1C, Lipid profile (Total cholesterol, HDL, TG, LDL, VLDL), Urine albumin (urine micral), urine creatinine, albumin/creatinine ratio (A/C ratio) values were measured before and after the study. These values are tabulated in Table 3.

Efficacy Parameters: T-test (unpaired) was performed for Urine albumin (urine Micral) for both groups (Telmisartan & Enalapril) and it was found to be highly significant with p values.

Telmisartan: At baseline the Mean urine albumin was (Mean – 81.9, SD – 30) and it was decreased at the end of

Table 1: Patient demographic characteristics of the study population (n=328)

CHARACTERISTICS	Telmisartan Group Values (Mean ± SD) (n=170)	Enalapril Group Values (Mean ± SD) (n=158)
Age (years)	51.1±10.4	48.1± 10.5
Males [n (%)]	80 (47%)	80 (51%)
Females [n (%)]	90(53%)	78 (49%)
Height (Cm)	157 ± 7.54	158.34±5.99
Weight (kg)	67.01± 10.68	66.5±12.1
BMI † (kg/m^2)	26.72± 4.94	26.4 ± 3.9

† Body –mass index is the weight in kilograms divided by the square of the height in meters.

Table 2: Mean differences of blood pressure and laboratory parameters in two drugs

	Telmisartan Group Values (Mean ± SD)		Enalapril Group Values (Mean ± SD)	
Characteristics	Baseline	End of study	Baseline	End of study
Blood pressure (mm Hg)				
Systolic	139.14±16.38	133.44±13.36	137.04 ± 14.9	129.01±12.58
Diastolic	84.17±9.76	82.01 ± 8.45	83.5 ± 8.6	80.7 ± 8.3
MAP ‡	102.5±10.3	99.1 ± 8.7	101.4 ± 9.5	96.8 ± 8.5
PP §	54.96±14.44	51.4 ± 11.6	53.4 ± 12.1	48.2 ± 10.6
FBS (mg/dl)	136.53±52.35	125 ± 44.5	141.8 ± 54.9	118.7 ± 43.3
PLBS (mg/dl)	216.25±67.81	199.06 ±61.13	215.9 ±64.04	187.8 ± 53.8
HbA1C (%)	8.18 ± 1.62	7.39 ± 1.34	8.32 ± 1.53	7.56 ± 1.31
Total Cholesterol?* (mg/dl)	183.05±61.15	164.32 ± 56.1	184.8 ± 45.2	174.95 ± 59.1
HDL ?* (mg/dl)	42.38 ± 4.64	44.2 ± 4.7	42.8 ± 4.3	43.28 ± 4.5
Triglycerides** (mg/dl)	150.06 ± 73.2	143.2 ± 60.6	162.18±82.29	159.92±100.7
LDL ?* (mg/dl)	108.4 ± 33.6	98.7 ± 27.5	120.44 ± 79.6	104.23±32.37
VLDL (mg/dl)	28.4 ± 9.2	27.4 ± 5.9	29.72 ± 10.73	30.62 ± 20.36

‡ The mean arterial pressure was calculated as diastolic arterial pressure + (systolic arterial pressure – diastolic arterial pressure) ÷ 3.

§ The pulse pressure was calculated as systolic arterial pressure – diastolic arterial pressure.

?* To convert values to micromoles per litre, multiply by 0.02586.

** To convert values to micromoles per litre, multiply by 0.01129.

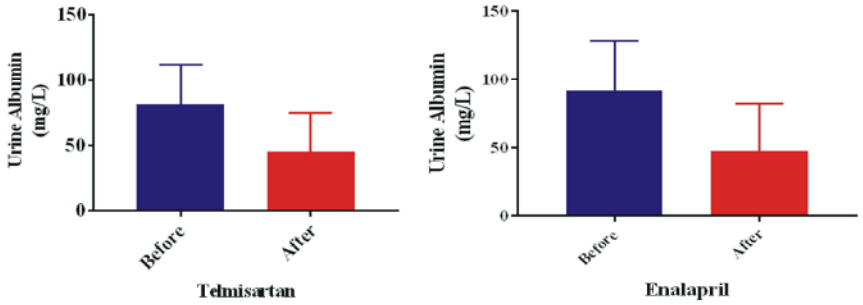

Fig. 2: Urine Albumin levels in two groups

the study (after treatment with the study drug) with an average of (Mean – 45.5, SD – 29.3) and this change was very significant.

Enalapril: At baseline the Mean urine albumin was (Mean – 91.38, SD – 36.29) and it was decreased at the end of the study (after treatment with the study drug) with an average of (Mean – 47.63, SD – 34.61) and this change was very significant. Urine albumin levels in two groups are given in Fig. 2.

At the end of the study the reduction in urine albumin is more with Enalapril (Mean difference 43.75 ± 4.003) when compared with Telmisartan (Mean difference 36.49 ± 3.23). The p values were < 0.05 for both groups and it was found that reduction of diabetic nephropathy in Enalapril treatment group at the end of the study statistically different from the Telmisartan treatment group. Mean difference of efficacy parameters in two drugs are given in Table 3.

Table 3: Mean difference of efficacy parameters in two drugs.

	Telmisartan Group Values (Mean ± SD)		Enalapril Group Values (Mean ± SD)	
Characteristics	Baseline	End of study	Baseline	End of study
Urine Albumin (mg/L)	81.9 ± 30.0	45.5 ± 29.3	91.38 ± 36.29	47.63 ± 34.61
Urine creatinine (mg/dl)	187.5 ± 75.8	163.2 ± 80.0	173.35±77.95	147.72±80.78
Albumin/Creatinine ratio (A/C ratio) (mg/g)	52.15 ± 31.8	31.7 ± 19.4	67.35±50.55	39.24 ± 44.82

DISCUSSION

Head- to- head comparison of renal outcomes with the use of an angiotensin II- receptor blocker (Telmisartan) and an ACE inhibitor (Enalapril) in subjects with type 2 diabetes and nephropathy was carried out, we determined that Telmisartan was not inferior than Enalapril in preventing the progression of renal dysfunction, measured as the decline in the urine albumin. A decline in the urine albumin is a key determinant of diabetic nephropathy.

There has been one clinical study that has directly compared the effect of angiotensin II- receptor blocker (losartan) with that of an ACE inhibitor (Enalapril) in subjects with type 2 diabetes and early nephropathy [4]. That short-term study indicated that both drugs reduced urinary albumin excretion; differences between the treatments were not significant. Three other studies have compared treatment with an angiotensin II- receptor blocker and an ACE inhibitor two in patients who had heart failure [5-7]. In these studies, the ACE inhibitor captopril, administered three times daily (titrated to a dose of 50 mg three times daily), was compared with once-daily losartan (50 mg) or twice-daily valsartan (160 mg). In all three trials, the two drug classes had an equivalent effect on the primary end point: the rate of death from all causes. The non-superiority of losartan was attributed to the low dose used, although this reason could not be cited in the study involving valsartan [7].

In our study, at the end the reduction in urine albumin was more with Enalapril (Mean difference 43.75 ± 4.003) when compared with Telmisartan (Mean difference 36.49 ± 3.23). The p values were < 0.05 for both groups and it was found that reduction of diabetic nephropathy in Enalapril treatment group at the end of the study is statistically differs than the Telmisartan treatment group.

Our study established that Enalapril confers strong renal protection in patients with type 2 diabetes and nephropathy.

End-stage renal disease continues to be a worldwide public health concern. Recent estimates by the National Institutes of Health indicate that diabetes represents the single largest cause of end-stage renal disease, accounting for approximately 40 % of all cases in the United States between 1994 and 1998 [8]. Furthermore, the incidence of end-stage renal disease in patients with type 2 diabetes is rising sharply in many regions of the world and is expected to double by 2010. The annual costs associated with end-stage renal disease in the United States reached $12 billion in 1998 and are expected to surpass $28 billion by 2010 [9]. Preventing or delaying the progression of diabetic nephropathy is therefore an essential management goal. We believe our findings go a long way toward achieving this goal and may also have an important economic effect.

CONCLUSIONS

The results of the present study reveal that all the two groups showed an improvement in diabetic nephropathy symptoms after 3 months of follow-up. All evaluated nephropathy efficacy parameters showed statistically significant improvements. In patients treated with Enalapril greater reduction of urine albumin was recorded when compared with patients treated with Telmisartan.

In conclusion, Enalapril confers strong renal protection in patients with type 2diabetes and nephropathy. Telmisartan is not inferior to Enalapril in providing Reno protection in subjects with Type 2 Diabetes and early nephropathy. This result is consistent with emerging data that support the clinical equivalence of angiotensin II- receptor blockers and ACE inhibitors in various conditions associated with high cardiovascular risk.

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