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ORIGINAL ARTICLE

COMPARATIVE EFFECT OF ENALAPRIL AND CATOPRIL IN NORMOTENSIVE PATIENTS WITH INCIPIENT DIABETIC NEPHROPATHY

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Abstract:

Objective- *To see the effect of enalapril and captopril on patients with diabetes and impending diabetic nephropathy.*
Material Methods- *Study was performed in patients suffering with long term diabetes mellitus. A total of 61 normotensive patients of diabetes having persistent microproteinurea were selectedwith age >30 years, Informed consent was taken from all patients and a strict compliance of the drugs during the study was ensured.The patients those selected were given enalapril 2.5 mg daily or captopril 25 mg daily in two divided doses or placebo for a period of three months.*
The dietary instructions and anti-diabetic treatment at the beginning of the trial remained unchanged during the study.
Results and Conclusion:- *Both captopril and enalapril reduced protenuria significantly as compared to the placebo group. Regarding the serum creatintine level there was no significant alteration in both groups as compared to placebo.*

KEYWORDS:

Diabetes mellitus, Nephropathy, Captopril, Enalapril, ACE inhibitors.

INTRODUCTION:

Diabetes mellitus, the most common endocrine disease, is characterized by disorders of metabolism of carbohydrates, proteins, fats, water and electrolytes as a consequence of absolute or relative deficiency of insulin in the human body (Mogensen et al. 1983). Diabetic nephropathy is a major microvascular complication of diabetes, representing the leading cause of endstage renal disease in the world, and a major cause of morbidity and mortality in both type 1 and type 2 diabetic subjects. Clinical hallmarks of diabetic nephropathy include a progressive increase in urinary albumin excretion and a decline in glomerular filtration rate (GFR), which occur in association with an increase in blood pressure, ultimately leading to endstage renal failure (Cooper, 1998; Giunti et al., 2006). It is interesting to note that the early nephropathy (microproteinurea) is preventable if it is detected and treated promptly (Viberti et al. 1982; Brayan et al. 1989). Several types of interventions have been proposed to prevent the persistent proteinurea in diabetics. Strict metabolic control achieved with portable insulin pumps can reverse glomerular hyperfilteration due to poor metabolic control and restriction of dietary protein can reduce albumin excretion in diabetics, but clinical data do not suggest that patients can comply with such a diet for long period. The present study was undertaken with the role evaluation of enalapril and captopril in the prevention of diabetic nephropathy in normotensive diabetics with persistent microalbuminurea with comparison of the relative safety profiles.

Title : COMPARATIVE EFFECT OF ENALAPRIL AND CATOPRIL IN NORMOTENSIVE PATIENTS WITH INCIPIENT DIABETIC NEPHROPATHY Source:Indian Streams Research Journal [2230-7850] R. R. SINGH , PRATAP SHANKAR , R. C. VERMA , AMODSACHAN AND R. K. DIXIT yr:2013 vol:2 iss:12

MATERIAL AND METHODS

Patient selection

A total of 61 normotensive patients of diabetes having persistent microproteinurea were selected from those attending medical outpatient department/diabetic clinic and/or admitted in various wards of L.L.R. and Associated Hospitals, Kanpur. Patients with age >30 years, diabetic for more than five years, non-hypertensive, having persistent microalbuminuria (albumin excretion rate 30-550 mg/day recorded at least three times over three months), and having stable metabolic control of diabetes were included for the study. While patients excluded those were hypertensive, postural hypotension, pregnant/lactating mothers, taking steroids, with thyroid disease/acromegaly/Cushing's syndrome, and sensitive to enalapril or catopril. Informed consent was taken from all patients and a strict compliance of the drugs during the study was ensured.

The study was conducted in two phases:

Phase – I: The diabetic patients who presented to us and were normotensive assessed for persistent microalbuminuria (albumin excretion rate 30-550 mg/day for at least three times) over three months period.
Phase – II: The patients those selected were given enalapril 2.5 mg daily or captopril 25 mg daily in two divided doses or placebo for a period of three months.

The dietary instructions and anti-diabetic treatment at the beginning of the trial remained unchanged during the study.

Grouping of the Patients

The 61 patients (37 male and 24 female) were divided in three groups

Group – I: Normotensive diabetics with microalbuminuria who were kept on placebo treatment (20 patients).
Group – II: Normotensive diabetics with microalbuminuria who were kept on enalapril 25 mg daily (21 patients).
Group – III: Normotensive diabetics with microalbuminuria who were kept on captopril 25 mg daily (20 patients).

STUDY DESIGN

All patients of normotensive diabetics with microproteinuria, recruited for the study have to be examined clinically as detailed history recording and physical examination and data collected was stored systematically in a predesigned proforma.

INVESTIGATIONS

All the patients recruited were follow investigation as Routine (Urine, TLC, DLC, ESR, Hb%), Specific (serum creatinine, serum Na/K, blood urea, blood glucose by glucose oxidase method as fasting and post prandial, ECG), special (estimation of microprotienuria by the technique of Fujita et al. 1984).

SIDE EFFECTS AND COMPLICATIONS

Each patient was closely questioned and observed regarding occurrence of any side effect or complications during the study.

STATISTICAL ANALYSIS

Mean and standard were calculated for each parameter. Data before and after administration of drug were compared by the Fisher's t-test and statistical significance was assigned to p-value of less than 0.05.

RESULTS AND OBSERVATIONS

The selected patients for study were divided in to three groups (according to the drug used) as Placebo group, enalapril group and captopril group. A detailed analysis of clinical and laboratory data of the aforesaid patients was performed and the observations are depicted in tubular form.

Majority of patients (61) in our study were found to be of middle socio-economic status closely followed by upper middle class. 53 patients (86.88%) gave a definite positive family history of diabetes while 8 patients (13.12%) were negative in family history of diabetes. All the patients under study belonged to NIDDM type of diabetes. Out of 61 patients, 53 were controlled by diet+oralhypoglycemics while 8 were controlled by diet alone.

The mean age of the placebo group was 54.83 ±9.20 years. Maximum cases belonged to the age group of 51-60 and 61-70 years. The male : female ratio was 1.5:1. The mean age of enalapril group was 54.83±9.20 years. Patients belonged to the age group of 51-60 years closely followed by 61-70 years with male female ratio of 1.62:1. And the mean age of captopril group was 52.60±9.57 years. Maximum patients belonged to the age group of 51-60 and 61-70 years with male female ratio of 1.5:1.

Tab. Comparison of the effect of Placebo, Enalapril and Captopril on microalbuminurea in normotensive diabetic patients

Groups	**Urine albumin (mg/24 hrs)**				**t**	**p**	**Inference**
	Pre-treatment		**Post-treatment**				
	Mean	±S.D.	**Mean**	±S.D.			
Placebo	173.93	±62.72	262.46	±95.87	3.45	<0.01	Moderately significant rise in albuminuria
Enalapril	176.54	±63.07	76.27	±28.59	6.47	<0.001	Highly significant decrease
Captopril	152.20	±68.47	68.82	±32.81	4.91	<0.001	Highly significant decrease

DISCUSSION:

The present study was conducted on normotensive diabetic patients with persistent microalbuminuria. The study was conducted on a total number of 61 patients out of which 37 were male and 24 were female with a male:female ratio 1.54:1. The mean age of the patients in our study was 53.47 ±9.25 years. All the patients were of NIDDM group and out of them 53 patients were controlled by oral hypoglycemic and diet while 8 patients were controlled by diet alone. The dietary instructions and anti-diabetic drug management was constant throughout the period of study. All the patients were normotensive with a mean systolic B.P. 132.23 ±4.76 mm Hg and a mean diastolic B.P. of 82.5 ±2.30 mm Hg before the study. Family study of diabetes was positive in 53 cases out of 61 patients (i.e. 86.88%). Most of the patients belonged to middle socioeconomic class (36.06%) and upper middle class (27.86%).

The study was conducted over three month period. The patients were studied in three groups.

Group – I: Placebo group –

We had 20 patients in this group with a mean age of 54.83 ±9.20. Beforetreatment the mean urinary albumin excretion rate was 173.93 ±62.72 mg/dl while after treatment with placebo the mean value of urinary albumin excretion rate was 262.46 ±95.87 showing a moderately significant rise of 88.53 ±33.15 mg/day in urinary albumin excretion in patients who were kept on placebo treatment ($t=3.45$; $p<0.01$). The mean systolic B.P. before treatment was 132.5 ±4.29 mm Hg as compared to the post treatment value of 133.0 ±3.27 ($t=0.41$; $p>0.05$ i.e. an insignificant change in systolic B.P. in those on placebo treatment). The mean diastolic B.P. before treatment in placebo group was 82.2 ±2.33 mm Hg while post-treatment value was 82.4 ±2.11 mm Hg ($t=0.41$; $p>0.05$ i.e. an insignificant change in diastolic B.P. in those on placebo treatment).

The pre-treatment value of serum creatinine was 1.22 ±0.18mg% as compared to post treatment

value of 1.30±0.16; t=1.50; p >0.05; insignificant change). Serum Na before treatment was 138.3±2.92 mEq/l. while post treatment value was 138.9±2.38 (t=0.71; p>0.05 insignificant change). The serum K also showed an insignificant change with a pretreatment value being 4.10±0.082 (t=1.92; p>0.05). The blood urea before treatment was 22.2 ±5.14 and after treatment it was 23.0 ±4.87 (t=0.50; p>0.05).

Group – II: Enalapril treated group –

In this group we had 21 patients with a mean age of 53.0 ±8.98. The patients were given enalapril 2.5 mg O.D. during the period of study. In this group, the urinary albumin excretion rate decreased from 176.54 ±63.07 mg/day to 76.27±28.59 mg/day i.e. a decrease of 100.27 ±34.48 mg/day (t=6.47; p<0.001 i.e. a highly significant change).

The systolic B.P. also decreased from a mean value of 132.5 ±4.67mm Hg to 123.10 ±3.86 mm Hg i.e. a decrease of 9.4 ±0.81 mm Hg (t=6.96; p<0.001 i.e. a highly significant change). The diastolic B.P. fell from a mean value of 82.8 ±2.46 mm Hg to 74.9 ±3.27 mm Hg i.e. a decrease of 7.9 ±0.81 mm Hg (t=8.68; p<0.001 i.e. a highly significant change).

The weight and the blood sugar values remained insignificantly altered during the treatment with enalapril. The pre-treatment weight was 62.45±8.06 kg and the post treatment weight was 62.55 ±8.02 kg (t=0.039; p>0.05). At six weeks from the start of treatment the fasting blood glucose was 105.3±3.13 mg/dl as compared to a pre-treatment value of 104.80 mg/dl (t=0.53; p>0.05; insignificant change). The post prandial blood glucose 2 hours after ingestion of 75 gm glucose was 147.80±6.18 mg/dl at the beginning of the treatment and six weeks thereafter the value was 149.0 ±5.82 (t=0.63; p>0.05; insignificant change). Similarly the fasting blood glucose after 12 weeks from the start of the study was 105.8±2.33 mg/dl as compared to 104.80 ± 2.78 mg/dl at the beginning (t=1.23; p>0.05; insignificant change). The post prandial blood glucose after 3 months from the start of the study was 149.0 ±7.09 mg/dl as compared to a pre-treatment value of 147.80 ±6.18 mg/dl (t=0.57; p>0.05; insignificant).

Enalapril treatment did not produce any significant change in serum creatinine value. The pre-treatment value of serum creatinine was 1.29±0.1099 and the post-treatment value was 1.33±0.10 (t=1.29; p>0.05; i.e. insignificant change). Similarly mean serum Na value before treatment was 141.10 ±2.10 mEq/l and after treatment it was 141.20 ±2.09 mEq/l (t=0.15; p>0.05 i.e. insignificant change). Mean serum K values before treatment was 3.73±0.17 mEq/l and after treatment it was 3.77±0.22 (t=0.086; p>0.05 i.e. insignificant change). The blood urea values also did not show any significant change after treatment with enalapril 2.5 mg O.D. Pre-treatment value was 26.70±6.13; while the post-treatment value was 27.20±5.12 (t=0.28; p>0.05; insignificant change).

Group – III: Captopril treated group –

In this group we had 20 patients with a mean age of 52.6 ±9.57. They were given captopril 25 mg daily in two divided doses. In this group the urinary albumin excretion rate decreased from a mean pre-treatment value of 152.20±68.47 mg/day to a mean post-treatment value of 68.82±32.81 mg/day i.e. a decrease of 83.38 ±35.66 mg/day (t=4.91; p<0.001; highly significant).

The systolic B.P. also decreased from a mean value of 131.70±5.32 mm Hg to 123.60 ±4.79 mm Hg i.e. a decrease of 8.1 ±0.62 mm Hg (t=5.12; p<0.001; highly significant). The diastolic B.P. decreased from a mean value of 82.5 ±2.13 mm Hg to 75.3 ± 2.61 mm Hg; i.e. a decrease of 7.2 ±0.48 mm Hg (t=9.6; p<0.001; highly significant).

The metabolic control of diabetes was stable during the study as shown by no significant change in fasting and post prandial glucose levels at different times during the study. The fasting blood glucose level before treatment with captopril was 104.10 ±2.93 mg/dl and at 6 weeks of treatment it was 104.3±3.57 mg/dl (t=0.19; p>0.05; insignificant change). The post-prandial glucose level 2 hrs after 75 gm glucose was 147.2±7.46 mg/dl at 6 weeks of treatment as compared to 147.0±7.18 mg/dl at the beginning of the treatment (t=0.086; p>0.05; insignificant change). Similarly, the fasting blood glucose after 12 weeks from the starts of the study was 104.6±2.83 mg/dl as compared to 104.10±2.93 mg/dl at the beginning (t=0.54; p>0.05; insignificant change). The post-prandial blood glucose 2 hrs after 75 gm glucose was 148.10 ±7.88 mg/dl at 12 weeks of treatment as compared to 147.0±7.18 mg/dl at the start of the study (t=0.46; p>0.05; insignificant change). Similarly the mean weight did not vary significantly. The pre-treatment mean weight was 64.9±4.82kg and the post-treatment value was 64.95±4.93 (t=0.032; p>0.05; insignificant).

Captopril treatment did not produce any significant change in serum creatinine values. The serum creatinine value before treatment was 1.22±0.18 mg% and the post-treatment value was 1.30±0.16 mg% (t=1.50; p>0.05; insignificant). Similarly serum Na value post-treatment was 138.9±2.38 mEq/l as compared to a pre-treatment value of 138.3±2.92 (t=0.71; p>0.05; insignificant change). Similarly serum K

value before treatment was 4.15±0.088 mEq/l as compared to 4.10±0.082 after treatment (t=1.92; p>0.05; insignificant change). The blood urea level also didi not change significantly during the study. The pre-treatment value was 22.2±5.14 mg/dl as compared to 23.0±4.87 mg/dl at the end of treatment (t=0.50; p>0.05; insignificant change).

Thus we see that both the ACE inhibitors i.e. enalapril and captopril reduced urinary albumin excretion by a statistically highly significant degree (p<0.001). Conversely, a moderately significant (p<0.01) rise in albumin excretion was seen with treatment in placebo group. Similar results were found by Marre et al. 1988 with enalapril. Moreover it may be noted that both the ACE inhibitors also caused a statistically highly significant fall in both systolic and diastolic B.P. The changes in albumin excretion could be attributed solely to change in blood pressure or inhibition of the converting enzyme or both. Other factors that may have affected these variables are changes in weight, protein intake, sodium balance, or metabolic control. There were discounted as weight, excretion of urea and sodium, and blood glucose concentrations were constant throughout the study.

Whether the inhibition of angiotensin converting enzyme has a specific effect on albumin excretion by reducing pressure within the glomeruli independently of its effects on systemic blood pressure, is a difficult question to answer. Insua et al. 1988 reported opposite effects on urinary albumin excretion in the presence of a similar fall in arterial pressure by nifedepine and captopril (urinary albumin excretion increased by 40% in the nifedepine group and decreased by 40% in the captopril group). A similar observation was made by Jackson et al. 1986 who showed that in diabetic ratsenalapril lowered the blood pressure and prevented the progression of proteinuria. In contrast to this treatment by verapamil, although producing a similar fall in arterial pressure, did not influence the progressive increase in proteinuria in diabetic rats. Similarly, Anderson et al. 1986 observed that in non-diabetic rats increase in proteinuria due to hypertension was prevented by enalapril but not by conventional anti-hypertensive treatment, though blood pressure was reduced equally in both treatments. Micropuncture data obtained by these investigators were in favor of a critical role of the decrease in intraglomerular pressure only produced by enalapril in the prevention of glomerular damage. Thus the ACE inhibitors seem to have an edge over other anti-hypertensives in the prevention of glomerular damage.

CONCLUSION

With all conclusive comments, study of enalapriland captopril we conclude that these drugs in low doses are well tolerated and relatively free of side effects and useful.

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