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Research Article

COMPARATIVE EFFICACY AND SAFETY OF ACE INHIBITORS AND ARBS IN PREVENTION AND PROGRESSION OF DIABETIC NEPHROPATHY

Richa Garg*[1]., Taruna Sharma[2]., Minakshi Dhar[3]., Monika Kakkar[4]., Dhasmana D C[5] and Navin Kumar[6]

[1,2,5]Department of Pharmacology, Himalayan Institute of Medical Sciences, SRHU, Dehradun
[3]Department of Internal Medicine, Himalayan Institute of Medical Sciences, SRHU, Dehradun
[4]Department of Biochemistry, Himalayan Institute of Medical Sciences, SRHU, Dehradun
[6]Department of Community Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005

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A B S T R A C T

Introduction: DN is one of the major complication of Diabetes Mellitus (DM), with high morbidity and mortality as well as major cause of end stage renal disease (ESRD). Early detection of DN and intervention in pre-clinical state can slow down disease progression thereby improving overall survival in patients with DN.
***Aims & Objectives*:** To compare the efficacy and safety of ACE inhibitors and ARBs in prevention and progression of diabetic nephropathy (DN).
***Materials & Methods*:** An interventional, analytical study being conducted in the department of Pharmacology, HIMS, Dehradun over a period of 12 months. 72 Patients fulfilling the inclusion criteria were recruited in the study by computer generated random number tables & specific baseline investigations like Serum Cystatin C & urinary albumin were done. Drug Ramipril 2.5-5 mg or Telmisartan 20-40mg on physician discretion was prescribed once daily for a period of 3 months after which specific investigations were repeated.
***Results* :** The average Pre and Post-therapy Serum Cystatin C levels for ACE Is and ARBs were 0.95±0.29 mg/dl, 0.73±0.23 mg/dl and 0.91±0.25 mg/dl, 0.73±0.26 mg/dl and urinary albumin levels were 154.37±74.27 mg/dl, 145.99±72.72 mg/dl and 150.60±58.63 mg/dl, 134.89±54.94 mg/dl respectively. ***Conclusion*:** ACE Is and ARBs were both found to be equally efficacious and safe. Post therapy Serum Cystatin C significantly declined suggestive of improved renal function in DN patients.

INTRODUCTION

Diabetes is a disease of complications. DN is one of the major complication of DM, with high morbidity and mortality as well as major cause of end stage renal disease (ESRD). Early detection of DN and intervention in pre-clinical state can slow down disease progression thereby improving overall survival in patients with DN. The diagnosis of DN and its progression is routinely based on tests like albumin creatinine ratio, urinary albumin [1], GFR and kidney function tests, but as such none of these tests are specific or sensitive indicators for the diagnosis and progression of DN.

The inadequacy of the traditional markers in detecting early changes in GFR and particularly in monitoring the course of advanced diabetic nephropathy calls for alternative non-invasive methods for early diagnosis and treatment.

Corresponding author:* **Richa Garg
Department of Pharmacology, Himalayan Institute of Medical Sciences, SRHU, Dehradun

A Bio marker called Serum Cystatin C (Sr Cys C) has been shown to give most accurate results for diagnosis, prevention, progression and early detection of renal injury in type 2 diabetic patients [2].

There is high-level evidence that its diagnostic sensitivity for the detection of even mildly impaired GFR, i.e; < 70 ml/min is far superior than the routine biomarkers used [3]. Its independence from height, gender, age, and muscle mass is an added advantage. By virtue of the fact that Sr Cys C diagnoses renal injury at a much earlier stage than any of the tests done routinely , it can have remarkably favourable impact on disease progression, patient survival and overall improved quality of life of the patient.

Interventions effective in slowing progression from microalbuminuria (MAU) to overt nephropathy include: (a) Strict glycemic control (b) Strict blood pressure control (c) Early intervention by drugs like ACEIs and ARBs and (d) Management of dyslipidemia [4]. Pharmacologic blockade of the renin-angiotensin system (RAS) slows down the

progression of DN. The proven efficacy of ACEIs and ARBs has made them first line agents for DN [5].

Owing to the fact that there are very few head to head comparative studies of these agents and secondly the lack of specific diagnostic biomarkers for early detection and timely initiation of therapy, this study was planned to compare the efficacy and safety of ACEIs and ARBs in the prevention and progression of DN on the basis of a biomarker Ser Cys C.

MATERIALS AND METHODS

This interventional, analytical study was undertaken in Himalayan Institute of Medical Sciences, Dehradun for a period of twelve months. Patients presenting to the Medicine OPD and primarily diagnosed with type 2 DM and fulfilling the inclusion criteria were recruited in the study, after obtaining written informed consent.

What this study adds

1. Early detection of DN by specific & sensitive biomarker Serum Cystatin C.
2. Slowing the progression of DN by early intervention by ACEIs & ARBs.

Selection of the Subjects

The patients were recruited on the basis of the following criteria:

Inclusion criteria

1. Patients with type 2 DM of duration > 5 yrs.
2. Patients on oral hypoglycemic drugs (for at least 5 yrs).
3. Stage 1 hypertensives (as per JNC7 criteria).
4. Urinary albumin of < 300 mg/L
5. Glycosylated Hemoglobin ≥ 7 %
6. Cystatin C levels at baseline < 1.09 mg/L

Exclusion criteria

1. Diabetes Mellitus type 1
2. On insulin therapy
3. Stage II hypertensives (as per JNC 7 criteria).
4. Any cardiovascular complications
5. Urinary albumin > 300 mg/L
6. ESRD
7. Any other co morbid conditions.

Study Protocol

The demographic profile and detailed history was obtained from each patient, which included personal and family history, history of diabetes in family, duration of diabetes and treatment history. A general physical examination was performed and BP, weight, height, waist and hip measurement, Body Mass Index was determined in all the patients and the findings were entered in a pre-designed case recording form.
Blood samples for baseline estimation of serum cystatin C [6] and HbA1c were drawn by experts in phlebotomy section under direct supervision. Urine was sent for urinary albumin estimation to the reference laboratory.

After the baseline results were obtained the patients were enrolled in the study in accordance with the inclusion criteria. They were randomly divided into two groups 36 patients in each, in accordance with the computer generated random number tables:

Group A: Ramipril 2.5-5 mg OD.
Group B: Telmisartan 20-40 mg OD.

The patients were periodically followed up every month for adherence to drug therapy and for any adverse drug reaction for a period of 3 months. At the end of three months repeat specific investigations - Serum Cystatin C, glycated haemoglobin and MAU were done. They were also enquired for presence of any adverse event due to prescribed drugs.
The treatment groups were compared and results were analysed by Microsoft excel 2010 and SPSS 19. The demographic profile of the study population like age, weight, height and BMI were expressed as mean ± standard deviation. The pre & post therapy comparison in the same group was done by paired 't' test and in between group comparison was done by un-paired 't' test. Descriptive analysis was represented by graphical representation, percentage, pie chart using Microsoft excel 2010.

RESULTS

Out of the total 72 patients in two groups A & B as shown in Table No. 1.

Table No 1 Demographic Profile of Patients in Study groupsA & B (n=72)
(All values are expressed in Mean ± SD)

Sr.No.	Parameters	Group A n=36	Group B n=36
1	Age (years)	50.97±9.53	53.36±10.38
2	Sex Distribution (M/F)	26/10	19/17
3	Height (m)	1.60±0.08	1.58±0.07
4	Weight (kg)	72.91±12.91	71.30±11.71
5	Body Mass Index (Kg/m^2)	28.46±4.77	28.50±4.16
6	Waist Hip Ratio	1.00±0.089	1.04±0.07
7	Duration of DM (years)	7.08±1.66	7.11±1.84
8	HbA1c (Baseline)	9.92±1.94	9.50±1.94
9	HbA1c (3months)	9.63±1.48	9.82±1.61

There were 45 male and 27 female patients (62.50% male and 37.50% female). The mean age of patients in group A & B was 50.97±9.53 & 53.36±10.38 years respectively and the mean WHR was 1.00±0.089 & 1.04±0.07 respectively. There was no significant difference between the groups with respect to mean age whereas WHR came to be highly significant ($P < 0.05$). The patients in Group A had mean weight of 72.91±12.91kg and in Group B it was 71.30±11.71kg. The BMI in Group A was 28.46±4.77 Kg/m^2 and in Group B it was 28.50±4.16 Kg/m^2 signifying that majority of the patients were overweight. This clearly denotes that weight is a major risk factor for increased prevalence of type 2 DM. Apart from WHR there was no significant difference between both groups with respect to mean age, height, weight, BMI and duration of Type 2 DM. This denotes that both the groups were comparable in characteristics.

Table No. 2, shows the Investigational details of the patients in study Group A that consisted of 36 patients. The mean BP at baseline and post therapy was 127.88±15.59 & 124.72±9.99 mm Hg respectively. Post therapy a decrease in Blood Pressure by 3.16 mm Hg was recorded, which was found to be significant with a P value of 0.019. Similarly, MAU at baseline and post therapy was 154.37±74.27 & 145.99±72.72 mg/l respectively. Post therapy, a decrease in MAU by 8.38 mg/l was recorded which was found to be significant with a P value of 0.003. In the same way Serum Cystatin C was also significantly reduced by 0.213 mg/l with a P value of 0.001.

The baseline and post therapy was 0.95±0.29 & 0.73±0.23 mg/l respectively.

Table No. 2 Pre & Post Therapy BP, MAU & Serum Cystatin C in Study Group A (n=36)

(All values are expressed in Mean ± SD)

Sr. No.	Parameters	At Baseline	Post Therapy (3 months)	Difference	p Value
1	Blood Pressure (mm Hg)	127.88±15.59	124.72±9.99	-3.16±5.6	0.019*
2	Microalbuminuria (mg/L)	154.37±74.27	145.99±72.72	-8.38±1.55	0.003*
3	Serum Cystatin C (mg/L)	0.95±0.29	0.73±0.23	-0.213±0.06	0.001*

Paired student t test

Table No. 3, shows the Investigational details of the patients in study Group B that consisted of 36 patients. The mean BP at baseline and post therapy was 132.27±16.87 & 127.77±11.24 mm Hg respectively. Post therapy a decrease in BP by 4.50 mm Hg was recorded which was found to be significant with a P value of 0.003. Similarly, MAU at baseline and post therapy was 150.60±58.63 & 134.89±54.94 mg/l respectively. Post therapy, a decrease in MAU by 15.71mg/l was recorded which was found to be significant with a P value of 0.001. In the same way Serum Cystatin C was also significantly reduced by 0.186 mg/l with a P value of 0.001. The baseline and post therapy was 0.91±0.25 & 0.73±0.26 mg/l respectively.

Table No 3 Pre & Post Therapy BP, MAU & Serum Cystatin C in Study Group B (n=36)

(All values are expressed in Mean ± SD)

Sr. No.	Parameters	At Baseline	Post Therapy (3 months)	Difference	p Value
1	Blood Pressure (mm Hg)	132.27±16.87	127.77±11.24	-4.50±5.63	0.003*
2	Microalbuminuria (mg/l)	150.60±58.63	134.89±54.94	-15.71±3.69	0.001*
3	Serum Cystatin C (mg/l)	0.91±0.25	0.73±0.26	-0.186±0.01	0.001*

Paired student t test

Table No. 4, shows the comparison of mean investigative values of study subjects in Group A & B. The baseline values denoting BP of Group A & Group B was recorded to be 127.88±15.59 & 132.27±16.87 mm Hg respectively with an intergroup difference of 4.38±1.28 mm Hg which was insignificant (P>0.05). Similarly, post therapy values denoting BP of Group A & Group B was recorded to be 124.72±9.99 & 127.77±11.24 mm Hg respectively with an intergroup difference of 3.05±1.25 mm Hg which was insignificant (P > 0.05). The baseline values denoting Serum Cystatin C of group A & B was recorded to be 0.95±0.29 & 0.91±0.25 mg/L respectively with an intergroup difference of 0.034±0.04 mg/L which was insignificant (P > 0.05).

Table No. 4 Pre & Post Therapy BP, MAU & Serum Cystatin C Study Groups A & B (n=72)

(All values are expressed in Mean ± SD)

Parameter	Group A	Group B	Group Difference	p value
	Blood Pressure (mm Hg)			
Baseline	127.88±15.59	132.27±16.87	4.38±1.28	0.280
Post Therapy	124.72±9.99	127.77±11.24	3.05±1.25	0.227
	Serum Cystatin C (mg/l)			
Baseline	0.95±0.29	0.91±0.25	-0.034±0.04	0.603
Post Therapy	0.73±0.23	0.73±0.26	-0.006±0.03	0.913
	Microalbuminuria (mg/l)			
Baseline	154.37±74.27	150.60±58.63	-3.77±15.64	0.812
Post Therapy	145.99±72.72	134.89±54.94	-11.10±17.78	0.469

unpaired student t test

Similarly, post therapy values denoting Serum Cystatin C of Group A & B was recorded to be 0.73±0.23 & 0.73±0.26 mg/L respectively with an intergroup difference of 0.006±0.03mg/L which was insignificant (P > 0.05). The baseline values denoting MAU of Group A & B was recorded to be 154.37±74.27 & 150.60±58.63 mg/L respectively with an intergroup difference of 3.77±15.64 mg/L which was insignificant (P > 0.05). Similarly, post therapy values denoting BP of Group A & B was recorded to be 145.99±72.72 & 134.89±54.94 mm Hg with an intergroup difference of 11.10±17.78 mm Hg which was insignificant (P > 0.05).

All patients were enquired for any adverse reaction occurring due to study drugs throughout the study period of three months. Overall, adverse effects were observed in 2 patients in Group A and none in group B. The predominant side effect was dry cough. Both the patients were switched to Group B.

DISCUSSION

DN is a progressively deteriorating kidney disease caused by damage to the capillaries in the glomeruli [7]. Early DN often has no symptoms. Clinical symptoms appear 5 to 10 years after significant kidney damage begins [8]. A decline in renal function, is assessed by MAU and Serum Cystatin C levels, of which Serum Cystatin C is regarded to be as a highly sensitive and specific marker for DN. It is now clear that the blockade of the RAAS not only reduces the BP but also slows the progression of renal disease in patients with DN [9]. RAAS has been targeted at different sites by various class of drugs. ACEIs reduces the production of Ang II by inhibiting the conversion of Ang I to Ang II by Angiotensin converting enzyme. ARBs on the other hand antagonize AT1 receptors and prevent Ang II from binding [10].

The preclinical diagnosis of renal injury was assessed by MAU. Due to which timely intervention was done, thus benefitting the patient in delaying the progression of the disease. Because of timely intervention by ACEIs and ARBs the MAU was significantly decreased to 142.36 mg/l from 156.12mg/l. In the 70.5% of the patients, at baseline had elevated levels of serum cystatin C with a mean of 129.48±69.78 mg/l. In 30.5% of these patients, it reverted back within normal range. This was because of the early intervention by ACEIs and ARBs.

No serious side effects were associated with either study groups. In both the study groups adverse effects were mild and there was no significant difference in both groups [11]. Cough was seen in two of the patients of ACE group which were then moved to ARB group.

To conclude, both the study groups significantly reduced the BP, MAU and Sr Cys C levels in type 2 diabetics with DN but there was no intergroup difference among the efficacy of both the study drug groups. The adverse effect profile was more or less similar in both the study groups [12]. This indicates the potential of these drugs in the treatment of type 2 diabetics with DN and may also retard the course of disease by decreasing the progression of the renal injury.

Limitations of the Study

1. ***Small sample size:*** The sample size could be increased so that the differences in response among the different racial groups could be evaluated.

2. ***Short follow up peiod:*** A long follow up period, to strengthen and reinforce the results of the study and also to observe the long term side effects of these drugs.
3. ***Glycemic control:*** The poor glycemic control throughout the study could have affected the results of specific tests.

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Conflicts of Interest

The authors declare that they have no competing interests.

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Ethics Committee Approval

Institutional Ethics Committee, HIMS, SRHU, Dehradun

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