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Original Research Paper

Pharmacology

A STUDY ON THE EFFECT OF LISINOPRIL & OLMESARTAN IN DIABETIC NEPHROPATHY

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ABSTRACT

Introduction: Nephropathy is a major cause of illness and death in diabetes. Excess mortality in diabetes occurs mainly in proteinuric type 1 and type 2 diabetic patients and most of the patient die due to cardiovascular complication than End Stage Renal Disease (ESRD) as such particularly in type 2 patient. DN is the single most common cause of ESRD all over world, accounting for 33%. Proteinuria is a key feature of DN and a strong predictor of speed of progression towards end stage renal failure.**Aims and Objective** :To evaluate and compare the efficacy of Angiotensin converting enzyme inhibitor and Angiotensin receptor blocker in controlling microalbuminuria of Diabetic Nephropathy.**OBESRVATIONS AND RESULT**64 cases fulfilling the criteria were choosen and studied. All the cases were randomized into either group (ACE-Is or ARB) and studied at the beginning and at the end of 3 months of treatment after subsequent follow up.There is no worsening/ deterioration of renal function due to treatment with either drugs.reduction in microalbuminuria in both males and females in both Lisinopril and olmesartan group.**Discussion**The study has shown that both the drugs – Lisinopril and Olmesartan reduce urinary albumin excretion and within the group,the reduction in microalbuminuria is considerable and significant. However, the difference in reduction of microalbuminuria when compared between the two groups is statistically insignificant.

KEYWORDS :

Introduction

The name 'Diabetes' comes from the Greek word for a syphon, the sweet taste of diabetic urine, was recognized at the first millennium,but the objective'Mellitus' (honeyed) was only added byJohn Rollo in the late 18th century.

Albuminuria was noted as a common abnormality in diabetic patient by Joslin in 1916,and the association of nodular glomerulosclerosis with nephritic syndrome in diabetes was reported in 1936 by Paul kimmelsteil and Clifford Wilson.In early stage of diabetic glomerulopathy, the glomerular filtration rate (GFR) is increased due to increased filtration surface area. Later decline in GFR is associated with an increase in the fractional mesangial volume and glomerular accumulation, which leads to decrease in the capillary filtering surface area.

In the early stage of diabetic renal disease, increased urinary albumin excretion (defined as microalbuminuria) is likely to results from increased capillary pressure-mediated transglomerular flux of albumin. As the degree of albuminuria worsen, progressive alteration of the glomerular filtration barrier, such as loss of negative charge and enlargement of pore size (possibly secondary to podocyte loss) take place.

Persistent albuminuria (300 mg/24 h) is the hallmark of diabetic nephropathy, which can be diagnosed clinically if the albuminuria 300 mg/24 h persist at least on two occasion 3 month apart, provided that there are no clinical or laboratory evidence of kidney or urinary tract disease other than diabetic glomerulosclerosis[1]. This clinical definition of Diabetic Nephropathy (DN) is valid in both type 1 and type 2 diabetes mellitus (T1DM & T2DM)

There are several longitudinal studies have shown that raised urinary albumin excretion below the level of clinical albuminuria, so called microalbuminuria, strongly predict the development of DN in both type 1[2] and type 2 diabetes mellitus[3] and also has a powerful association with microvascular disease[4].

The prevalence of arterial hypertension in type 2 diabetes mellitus patient was higher 48%, 68%, 85% in the normalbuminuric, microalbuminuric and macroalbuminuric group respectively[5].

Oxidative stress is widely recognized as a key component in the development of diabetic complication. AGEs have long been associated with increased oxidative stress both in vitro and vivo.

Manoeuvers that lessen proteinuria have significant renoprotective effect. Excessive protein overload appears to induce tubuler-interstitial damage and hence contribute of disease progression.

According to MOGENSEN et al[8], DN is divided into 5 stages: -

(1) Early hypertrophy stage- increase in renal plasma flow and GFR.
(2) Silent stage- subtle morphological changes including thickness of glomerular basement membrane,glomerular hypertrophy,mesangial and tubulointerstitial expansion.
(3) Incipient stage- microalbuminuria
(4) Overt stage- Dipstick positive proteinuria
(5) End stage renal disease with uremia

The earliest clinical evidence of DN is microalbuminuria. The expansion of mesangium due to accumulation of extracellular matrix correlates with clinical manifestation of DN.Good evidences supports the benefit of blood sugar and blood pressure control as well as inhibition of renin angiotensin aldosterone system (RAAS) in retarding the progression of DN.The key mechanism for efficacy of angiotensin converting enzyme inhibitor (ACE-Is) and angiotensin receptor blockers (ARBs) is reducing glomerular efferent arteriolar resistance, improved intrarenal hemodynamics resulting reduction of intraglomerular pressure.There is decrease in number and activity of interstitial monocyte. Subsequently the progression of tubulointerstitial fibrosis and tubular atrophy slowed down and thus helpful in suppression of diabetic nephropathy.

Several studies in the past have shown that antihypertensive therapy with different types of drug can reduce microalbuminuria or clinical proteinuria and retard the progression towards End stage renal failure.

Concerning the choice of antihypertensive agent, a new argument was introduced by some studies suggesting disparate renal protective effect of different drugs in animal studies and human. ACE-Is and ARBs exerts a specific antiproteinuric effect even without significant change in systemic blood pressure.

ACE-Is block the generation of angiotensinII, a potent inducer of intrarenal vasoconstrictor.Furthermore, ACE-1 increases level of vasodilatory prostaglandin PGI-2 and PGE-2 through inhibition of kinase II, an enzyme identical to ACE. Therefore these agent dilate both efferent and afferent arteriole, consequently reducing glomerular capillary pressure, since they preferentially dilate efferent over afferent[9], a fall in systemic blood pressure cause greater decrease of glomerular capillary pressure.

Lisinopril which is lysine derivative of Enaliprilate, an ACE-Is, its antihypertensive effect thought to be through the renin-angiotensin – aldosterone system (RAAS) even in patient with low renin hypertension.

Olmesartan medoxomil is an inactive ester prodrug that is completely hydrolyzed to the active form, Olmesartan, during absorption from the gastrointestinal tract.

Lisinopril and Olmesartan produce minimal adverse effect on renal function in both patient with normal renal function and those with pre- existing renal impairment.

There is a need for head to head comparision of Angiotensin converting enzyme inhibitor and angiotensin receptor blocker in diabetic nephropathy.

On the background of these fact I planned to study the renal function in DN patients and to evaluate the effect of ACE-Is comparing with ARBs concerning the factors contributing in progression or aggravation of DN.

AIMS AND OBJECTIVE

To evaluate and compare the efficacy of Angiotensin converting enzyme inhibitor and Angiotensin receptor blocker in controlling microalbuminuria of Diabetic Nephropathy.

(1) To observe the effect of Lisinopril & Olmesartan onblood urea
(2) To observe the effect of Lisinopril & Olmesartan on serum creatinine
(3) To observe the effect of Lisinopril & Olmesartan on 24-h urinary Protein.

Study Setting :

The subjects' screening and recruitment was carried out at the Outdoor and Indoor of medicine department Anugrah Narayan Magadh Medical college and hospital Gaya, data, management, analysis and report preparation were carried out at the Department of Pharmacology, ANMMC Gaya.

Study Design: The current study had been designed as a post-registration (Phase IV), prospective, single blind, randomized controlled study with two parallel treatment groups.

The study consisted of a minimum of 1 (one) week pre-treatment period (washout period) followed by 3 month active treatment period..

Study Duration :

The duration of the study was 3 month for each subject from the commencement of study medications. No follow up was envisaged after this period. However, serious adverse events coming to the notice of the investigator for one week following termination was documented.

Subject selection criteria:

Screening for eligibility of the subject was performed on the very first visit, based on the following criteria.

Inclusion Criteria :

Subjects aged 30 yrs. to 65 yrs, both male and female were included in the study.

Exclusion criteria:

*Type 1 Diabetes Mellitus
*Overt proteinuria
*History of Hypertension
*History of coronary disease
*Non Diabetic renal disease
*Conditions known to be contraindications to the use of angiotensin receptor blockers- obstructive valvular heart disease, impaired renal function (serum creatinine>3mg %)
*Impaired liver function (AST or SGOT, ALT or SGPT and Serum Bilirubin three times upper limit of normal values).

*Serious severe systemic disease of any other organ system e.g. severe bone narrow failure, severe chronic obstructive pulmonary disease, acute neurological diseases etc.

*Known hypersensitivity to any of the trial medications or excipients in the formulation.

*Subjects who are concomitantly receiving following medications: any other antihypertensives, antiarrhythmics, aspirin 325 mg/day, non-steroidal anti inflammatory drugs, sedative, hypnotic or psychotropic drugs on regular basis.

Any other drug known to interact with or alter the response to trial drugs.

*Known or suspected alcohol or substance abuse.
*Participation in any other clinical drug trial within past one month.
*Any condition mental or physical, that in the opinion of the investigator would compromise the safety of the subject.

STUDY METHODOLOGY:

Each subject required at least five visits to the hospital during the study.During the first visit the subject was spotted.

If the subject was a newly diagnosed case of Diabetic Nephropathy with Microalbuminuria this visit also served as a screening visit, Otherwise a separate screening visit was set up after withdrawing existing medication/or interacting drugs and a washout period of minimum one (1) week given.

The study medication was started 1 week after screening visit. This was baseline visit. In cases of reluctance to attend every week, but satisfying all other conditions of screening criteria for eligibility, the screening visit and baseline visit was the same and study medication started.

Subsequent visits were at 3 weeks intervals. The final (end of study) visit was 3 month after three such follow-up visits.

Study termination

For an individual subject the study would be terminated in the circumstances noted below.On completion of 8 weeks of study medication as per protocol.

- In the event of an adverse event deemed serious enough to warrant withdrawal.
- In the event of protocol violation by study subject e.g. use of non-permitted concomitant medication.
- If the subject is lost to follow-up.
- Any other situation which, in the opinion of the project clinician, is not conducive to further continuation of the subject in the study.

Statistical Analysis:
Paramatric data was compared by the Student's test, with $p<0.05$ as the cut-off level for statistical significance.

Adverse events data was analysed by descriptive statistics.

OBESRVATIONS AND RESULTS

64 cases fulfilling the criteria were choosen and studied. All the cases were randomized into either group (ACE-Is or ARB) and studied at the beginning and at the end of 3 months of treatment after subsequent follow up.

Table – 1 : Age (in Years)* Gender in the two groups

		Gender		
		Male	Female	Total
Lisinopril	Mean	59.28	51.27	55.27
	N	14	18	32
	SD	5.24	7.41	6.32
Olmesartan	Mean	55.16	46.5	50.83
	N	18	14	32
	SD	8.2	16.24	12.22

Table 1 shows comparision of age (* gender) in the 2 groups. p value is P = 0.19

Figure 1: Scatter diagram showing age distribution in 2 groups

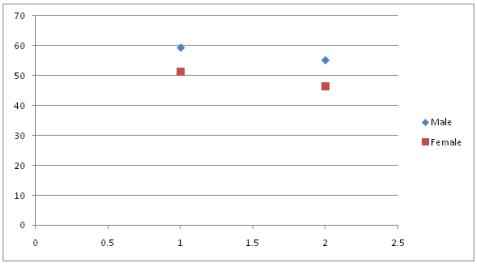


Table – 2 : Height (in Centimeters)* Gender in the two groups

		Gender		
		Male	Female	Total
Lisinopril	Mean	162.35	159	160.67
	N	14	18	32
	SD	7.77	5.91	6.84
Olmesartan	Mean	162.11	154.78	158.44
	N	18	14	32
	SD	3.79	3.21	3.5

Table 2 shows comparision of height (* gender) in the two Groups .P value is P= 0.24

Table – 3 : Weight (in kilograms)* Gender in the two groups at start of the treatment and at end of the treatment

		At the start			At the end of 3 month		
		Male	Female	Total	Male	Female	Total
Lisinopril	Mean	66.07	58.77	62.42	65.85	58.5	62.17
	N	14	18	32	14	18	32
	SD	12.2	6.94	9.51	10.31	11.73	9.1
Olmesartan	Mean	61.88	55.14	58.51	61.5	55.14	58.32
	N	18	14	32	18	14	32
	SD	5.28	5.47	5.37	5.10	5.47	5.28

Table – 3 shows comparision of weight in the two groups at the start and at the end of treatment trial .P = 0.14 at the start of trial.
P = 0.13 at the end of 3 month.

Table – 4: BMI * Gender in the two groups at start of the treatment and at end of the treatment .

		At the start			At the end of 3 month		
		Male	Female	Total	Male	Female	Total
Lisinopril	Mean	25.30	23.37	24.33	25.21	23.25	24.23
	N	14	18	32	14	18	32
	SD	3.16	3.19	3.17	3.16	2.94	3.05
Olmesartan	Mean	23.12	23.69	23.40	23.12	23.5	23.31
	N	18	14	32	18	14	32
	SD	1.87	2.69	2.28	1.82	2.69	2.25

Table 4 shows comparision of body mass index in the two groups at the start and end of the trial.p-0.53

Table 5:Biochemical Parameters in the two group at the start of treatment.

	Lisinopril		Olmesartan		P –
	Mean	SD	Mean	SD	
Fasting Plasma Glucose	195.46	72.87	172.46	62.82	0.24
Postprandial Plasma Glucose	251.18	78.1	271.5	77.66	0.36
Cholesterol	220.31	33.25	217.37	42.74	0.79
Triglycerides	136.18	28.03	136.59	0.05	0.96
HDL	43.62	3.62	42.37	4.23	0.27
LDL	138.31	22.75	133.71	33.72	0.57

Table 5 shows that the lipid profile were comparable in both groups.

Table 6:Biochemical Parameters in the two group at the end of 3 month.

	Lisinopril		Olmesartan		P – Value
	Mean	SD	Mean	SD	
Fasting Plasma Glucose	136.21	22.64	138	22.57	0.78
Postprandial Plasma Glucose	183.59	31.46	181.09	22.86	0.75
Cholesterol	213.5	34.17	213.78	37.47	0.98
Triglycerides	136.21	38.1	134.21	23.44	0.79
HDL	45.15	3.87	43.62	4.5	0.21
LDL	136.46	21.48	134.65	17.91	0.75

Table 6 shows that the lipid profile were comparable in both groups.

Table 7 :Renal Parameter in two groups

		Lisinopril		Olmesartan		P - Value
		Mean	SD	Mean	SD	
Start of Treatment	Urea	27.31	4.63	27.43	4.17	0.92
	Creatinine	0.97	0.14	0.97	0.14	1
At the end of 3 month	Urea	26.87	4.91	27.28	3.88	0.75
	Craetinine	0.96	0.13	0.96	0.17	1

Table 7 shows renal parameters in the two groups.
There is no worsening/ deterioration of renal function due to treatment with either drugs.

Figure 8 : Bar diagram showing Renal parameters in both group

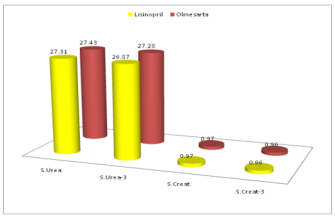


Table 9 : Blood Pressure and Microalbuminuria before treatment.

	Lisinopril		Olmesartan		P-Value
	Mean	SD	Mean	SD	
Systolic Blood Pressure	131.84	6.53	129.92	8.66	0.4
Diastolic Blood Pressure	82.62	6.63	79.31	5.1	0.28
24 Hour microalbuminuria	141.42	81.69	143.30	79.17	0.87

Table 9shows Blood pressure (both systolic and Diastolic) were in normal range before treatment.

Microalbuminuria at the start of treatment were comparable (no statistically difference) in both group.

Figure 10 : Bar diagram showing blood pressure in both group

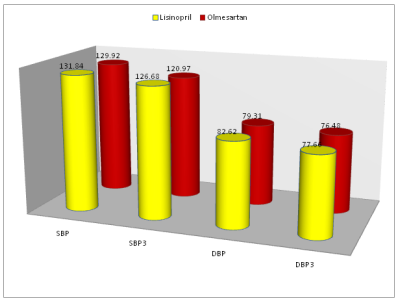
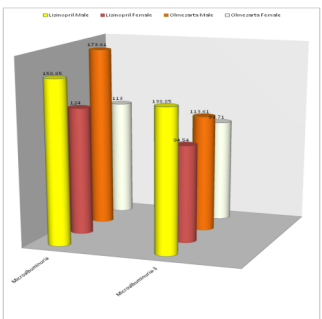


Table 11 : Microalbuminuria (mg/24 hour urine) * Gender in the two groups

		AT THE START			END OF 3 MONTH		
		MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
LISINOPRIL	MEAN	158.85	124	141.42	138.85	94.54	116.42
	N	14	18	32	14	18	32
	SD	60.13	96.95	78.54	56.16	82.80	69.48
OLMESARTAN	MEAN	173.61	113	143.30	113.61	99.71	106.66
	N	18	14	32	18	14	32
	SD	76.90	77.99	77.44	58.84	77.69	68.26

Table 11 shows reduction in microalbuminuria in both males and females in both Lisinopril and olmesartan group

Figure 12 : Bar diagram showing microalbuminuria in two groups



DISCUSSION

A decline in the glomerular filtration rate is a key derterminant of end stage renal disease.Preventing (or delaying) the development of microalbuminuria is a key treatment goal for renoprotection. Recent clinical trials suggest that the inhibition of the Renin – Angiotensin System (RAAS) may actually prevent nephropathy.The post hoc analysis of the reduction in hypertension in the Heart Outcome Prevention Evaluation Study and in the Losartan Intervention for Endpoint Study, found a lower incidence of overt nephropathy in subjects with type 2 diabetes who received therapy that inhibited the rennin – angiotensin system that in controls.

Trials have supported the clinical equivalence of Angiotensin II – receptor blockers and ACE inhibitors in delaying the progression of nephropathy in type 2 diabetes and in conditions that place them at high risk for cardiovascular events.

There has been a clinical study that has directly compared the effect of an Angiotensin II receptor blocker (Olmesartan) with that of an ACE inhibitor (Lisinopril) in subjects with type 2 daibetes and early nephropathy.

The present study is a similar study making head –to- head comparision of ACE-I (Lisinopril) and ARBs (Olmesartan) in the regression of microalbuminuria in type 2 diabetic nephropathy.

The study has shown that both the drugs – Lisinopril and Olmesartan reduce urinary albumin excretion and within the group,the reduction in microalbuminuria is considerable and significant. However, the difference in reduction of microalbuminuria when compared between the two groups is statistically insignificant.

Further, the study shows that Olmesartan had better reduction in systolic blood pressure , as compared to the reduction seen with Lisinopril though no significant difference was seen in the reduction of diastolic blood pressure . Despite this difference on blood pressure , both the drugs have shown reduction in microalbuminuria which supports the fact that reduction in microalbuminuria is independent of the antihypertensive action of the Lisinopril or Olmesartan.

The study also shows that antihypertensive treatment reduces microalbuminuria an decreases the progression of albuminuria in normotensive patients.

This was a small study (64 subjects) done ever a short follow up period of three month duration. The two drug classes had an equivalent effect on the end point i.e. Microalbuminuria reduction.

Our data indicate that Olmesartan is not inferior to Lisinopril in providing renoprotection in subjects with type 2 diabetes and early nephropathy.This results is consistent with emerging data that support the clinical equivalence of Angiotensin II receptor blocker and ACE inhibitors in various conditions associated with high cardiovascular risk.

Conclusion

This study shows that both Lisinopril (Angiotensin Converting Enzyme Inhibitor) and Olmesartan (Angiotensin II Receptor blocker) reduced urinary albumin excretion ; the difference between the two treatment regimen are not significant.

Olmesartan is not inferior to Lisinopril in providing renoprotection in subjects with type 2 diabetes and early nephropathy.

Olmesartan showed significant reduction in both systolic blood pressure, though not much reduction was seen with Lisinopril. Despite this both drugs have shown reduction in albuminuria which supports the fact that reduction in microalbuminuria is independent of the antihypertensive action of the Lisinopril or Olmesartan.

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