Irbesartan in Hypertensive Non Diabetic Advanced Chronic Kidney Disease : Comparative Study with Losartan

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Abstract

Background: Antihypertensive, Reno protective, antiproteinuric and cardioprotective effect of Angiotensin Receptor Blocker (ARB) is well proved in diabetic and nondiabetic nephropathy but not free of side effect in Advanced Chronic Kidney Disease (ACKD) patients. Most studies with ARB done on diabetic patients and some showed controversial result. Our aim is to compare the effects of two ARB (Losartan and Irbesartan) on hypertensive, nondiabetic ACKD patients.

Materials and methods: Nondiabetic patients with ACKD (CrCl< 30 ml/min) attended in medicine and Nephrology Department of Chittagong Medical College Hospital (CMCH) from March 2013 to May 2014 were enrolled in a prospective longitudinal study with 1:1 randomization.

Results: Among them 14 were male and 16 were female. Most patients were house wife, primary educated and nonsmoker. Chronic Kidney Disease (CKD) of 17 patients was due to Glomerulonephritis (GN) and in rest 13 was due to hypertension (HTN). Ingroup A: 15 patients received Losartan once daily with dose 50-100 mg/day. In group B: 15 patients received Irbesartan mono dose 150-300 mg/day. We studied Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Pulse Blood Pressure (PBP), renal function (CrCl), Proteinuria, Serum K^+ and serum uric acid at month 0, 3, 6, 9 and 12. At 12 months comparing group A and group B we found SBP decreased 20.93% Vs 19.85%, DBP decreased 12.84% Vs 15.03%, PBP decreased 30.05% vs 25.73%, CrCl reduced 6.99% Vs 10.81%. Proteinuria diminished 14.30% Vs 19.09%, serum K+ increased 26.58% Vs 12.07% (Statistically significant, p = 0.016) and Uric acid decreased 30.65% Vs 5.37% (Statistically significant, p<0.01).

Conclusion: Losartan in hypertensive nondiabetic ACKD compared with Irbesartan showed similar blood pressure control, similar effect on CKD progression and similar antiproteinuric effect. On the other side, Irbesartan showed less increase serum K+ but less decrease serum uric acid in comparison with Losartan.

Key words: Kidney disease; Hypertension; Irbesartan; Losartan.

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Submitted on : 12.11.2023
Accepted on : 03.02.2024

Introduction

Arterial Hypertension (AHT) is common in Chronic Kidney Disease (CKD) patient. It is an important morbidity and mortality factor in CKD. Besides AHT CKD also present as biochemical abnormality initially and uraemic features subsequently. Several drugs may be used to control hypertension in CKD. Some of them have shown their potential for slowing the progression of renal failure and proteinuria. Angiotensin II Receptor Antagonists (ARA II) have been successfully used in patients with AHT and nephropathy of both diabetic and nondiabetic origin, reducing proteinuria and with a favourable effect on renal failure progression.[1-5]

ARA II, both irbesartan and losartan inhibit the renin angiotensin system by selectively blocking the AT_1 subtype of angiotensin II receptor.[6] Irbesartan is a long acting AT_1 blocker that does not require biotransformation for its pharmacologic activity.[7] But the losartan require transformation to its active metabolite EXP3174.[8,9] Oral bioavailability of irbesartan is (60 to 80)% and absorption is unaffected by food but losartan is approximately 33% bioavailable with nearly 14% of administered dose being converted to active metabolite.[10-12] Food slightly delays absorption of losartan.[13] The plasma clearance of losartan and EXP3174 is 600ml/min and 50ml/min respectively. This clearance is mainly renal 75% and partly hepatic (25%). The dose of losartan is once or twice

daily.[14] Irbesartan is mainly cleared through the liver (78%) and in lower amount through the kidney (22%).[15] So, dose adjustment not required in advanced CKD.[16] The dose of irbesartan is once daily.[14] The efficacy of irbesartan and losartan is same and both used in CKD.A study on mild to moderate hypertensive patients showed that irbesartan reduces systolic and diastolic blood pressure more than losartan.[17] Another study on healthy subjects showed that losartan significantly reduces serum uric acid and increases urinary uric acid levels whereas irbesartan does not.[18] A study on type 2 diabetes and nephropathy showed that irbesartan reduced proteinuria and slowed progression to end stage renal disease. However, role of losartan was not assessed in this study.[19] Little study information is available on the effect of losartan and irbesartan in nondiabetic hypertensive CKD patient. There is no comparative study between losartan and irbesartan or hypertensive and diabetic CKD patient. To address these two topics a longitudinal randomized study was done to find out the comparative effect of losartan and irbesartan on hypertensive non diabetic advanced CKD patient.

Selecting proper antihypertensive we can reduce the morbidity and mortality in advanced CKD by controlling AHT, proteinuria and renal failure progression. It will be cost effective if proper drug is selected. We did the study to determine whether losartan is equally effective as irbesartan in hypertensive non diabetic advanced CKD patient.Our study will represent the scenario of comparative efficacy of both drug in large proportion of people of southern part of Bangladesh. Our aim is to compare the following effect of losartan and irbesartan:Antiproteinuric effect, antihypertensive effect, antiuricaemic effect and progression of kidney disease. If we can achieve same or more efficacy by losartan than irbesartan, it will be more beneficial because losartan is cheaper than the irbesartan.

Materials and methods

Our study was designed as a longitudinal study with 1:1 randomization. The place was in Medicine and Nephrology Department of Chittagong Medical College Hospital, Chattogram between period of 3rd March 2013 to 2nd May 2014. Total 106 patients admitted in above mentioned place with history of "hypertension and CKD" were evaluated. Among them 30 patients of "Hypertension with CKD"fulfilling inclusion criteria were enrolled. All hypertensive non diabetic ACKD patients admitted during study period and given consent to take part under study were included. Patients who refused to given consent, who were hyperkalemic, on dialysis, AKI on CKD or nonadvanced CKD (Stage I, II & III) were excluded from the study.

Diagnosed CKD patients were thoroughly informed about the detailed procedure of the study before examination and investigation. Patients allowed freedom to withdraw from the study even after participation. After getting written consent clinical history from eligible subject was taken and clinical examination done. Blood pressure of all patients were measured by mercury sphygmomanometer in sitting position ensuring 5-10 minutes bed rest. The mean of the three measurement was calculated and recorded as SBP and DBP. All relevant investigations done in Clinical Pathology Department of CMCH. UTP was measures after collecting 24 hrs urine (8 am of first day after discarding the first sample, upto 8 am of the next day including the night sample). Fasting venous sample was collected for blood glucose and other biochemical investigations. Fasting blood glucose, serum creatinine, serum uric acid, serum potassium and UTP were assessed by NOVA4^{+} automated clinical chemistry analyser, Jaffe, Uricase/PAP, Analyzer easylyte and biurette method respectively. After measuring blood pressure and doing investigations initial enrolment done only eligible (By inclusion and exclusion criteria) patients. Pre-test or initial blood pressure and other investigation reports were recorded in data collection sheet. Follow up done for recording data similar to pre-test at 3,6,9 and 12 months. After initial measurement patients selected for first patient was selected for intervention by losartan and irbesartan as 1:1 randomization. First patient was selected for losartan 50 mg daily by lottery method. Next patient received irbesartan 150mg daily. For, some patients this losartan or irbesartan was an additional antihypertensive along with previous antihypertensive on which blood pressure was not controlled. During follow up some patients dropped out due to refusal to continue the study,

shifting to dialysis treatment, Sudden death and missing due to unknown cause. Finally, data of 30 patients (15 patients received losartan and 15 patients received irbesartan) were collected, tabulated and analysed. Outcome of intervention were assessed mainly with regards to SBP,DBP, Creatinine clearance, 24 hours UTP, Serum potassium and serum uric acid. Data were processed and analysed by using computer bases software SPSSV.18.0. Different statistical methods were applied for data analysis. 'p' value was considered as statistically significant when it is less than 0.05.

Results

Out of 30 patients of this study male female ratio was almost equal. Most patients were secondary or higher educational status, housewife and non-smoker. Significant of them were in age group ≤50 years. GN CKD patients were more than HTN, CKD in both groups receiving losartan or irbesartan.

Table I Distribution of socio-demographic variables and diagnoses among the study groups (with χ^2 test significance) (n = 30)

Socio-Demographic Variables		Study Groups			
		Group A (Losartan) (n = 15)	Group B (Irbesartan) (n = 15)	Total (n = 30)	p Value
Sex	Male	4 (26.7)	10 (66.7)	14 (46.7)	1.000 NS
	Female	11 (73.3)	5 (33.3)	16 (53.3)	
Age Groups	> 50 Years	6 (40.0)	6 (40.0)	12 (40.0)	0.028 S
	≤ 50 Years	9 (60.0)	9 (60.0)	18 (60.0)	
Occupation	House Wife	11 (73.3)	5 (33.3)	16 (53.3)	0.080 NS
	Service Holder	1 (6.7)	7 (46.7)	8 (26.7)	
	Farmer	2 (13.3)	2 (13.3)	4 (13.3)	
	Businessman	1 (6.7)	1 (6.7)	2 (6.7)	
Educational Status	Illiterate	4 (26.7)	4 (26.7)	8 (26.7)	0.429 NS
	Primary	3 (20.0)	6 (40.0)	9 (30.0)	
	Secondary & Higher	8 (53.3)	5 (33.3)	13 (43.3)	
Smoking Status	Smoker	6 (40.0)	6 (40.0)	12 (40.0)	1.000 NS
	Non-Smoker	9 (60.0)	9 (60.0)	18 (60.0)	
Diagnoses	Glomerulo-nephritic CKD	7 (46.7)	10(66.7)	17(56.7)	0.269 NS
	Hypertensive CKD	8(53.3)	5(33.3)	13(43.3)	

In our study after 12 months therapy SBP decreased in group A (20.93 ± 9.26)% and in group B (19.85 ± 9.49), DBP decreased in group A (12.84 ± 6.65)% and in group B (15.03 ± 7.15)%, Pulse BP decreased in group A (30.05 ± 19.03)% and in group B (25.73 ± 17.39)%.

Table II Statistics of systolic, diastolic and pulse blood pressure between the study groups (With independent samples t- test significance)

Time	Study group A (n=15) Vs Study group B (n=15)		
	Systolic Blood Pressure (Mean ± SD)	Diastolic Blood Pressure (Mean ± SD)	Pulse Blood Pressure (Mean± SD)
Initial	172.67±19.54 Vs	98.00±3.68 Vs	74.67±18.17 Vs
	171.33± 28.44	100.00±13.76	71.33± 19.22
	$p=0.882^{NS}$	$p=0.594^{NS}$	$p=0.629^{NS}$
After 3 months	159.33± 12.80 Vs	91.67± 4.50 Vs	67.67± 12.66 Vs
	157.67±25.63	93.33 ±10.63	64.33 ±17.91
	$p=0.823^{NS}$	$p=0.583^{NS}$	$p=0.561^{NS}$
After 6 months	150.33±9.54 Vs	89.33±6.78 Vs	61.00±11.53 Vs
	150.67 ± 22.35	90.00±8.45	60.67 ±16.89
	$p=0.958^{NS}$	$p=0.813^{NS}$	$p=0.950^{NS}$
After 9 months	142.00±12.65 Vs	87.00±6.49 Vs	55.00±10.86 Vs
	146.00 ±18.54	87.33±8.21	58.67± 13.29
	$p=0.496^{NS}$	$p=0.903^{NS}$	$p=0.415^{NS}$
After 12 months	135.33±11.57 Vs	85.33±6.11 Vs	50.00± 9.82 Vs
	135.33±12.02	84.33±7.76	51.00 ±10.72
	$p=1.000^{NS}$	$p=0.698^{NS}$	$p=0.792^{NS}$
Percent decrease	20.93±9.26 Vs	12.84±6.65 Vs	30.05±19.03 Vs
	19.85 ±9.49	15.03±7.15	25.73 ± 17.39
	$p=0.756^{NS}$	$p=0.393^{NS}$	$p=0.521^{NS}$

● NS = Not Significant (p > 0.05).

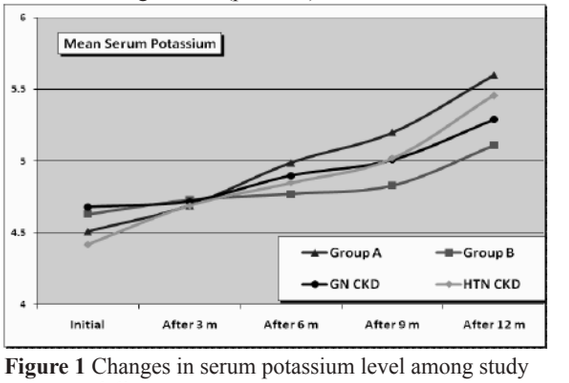

Figure 1 Changes in serum potassium level among study groups and diagnoses

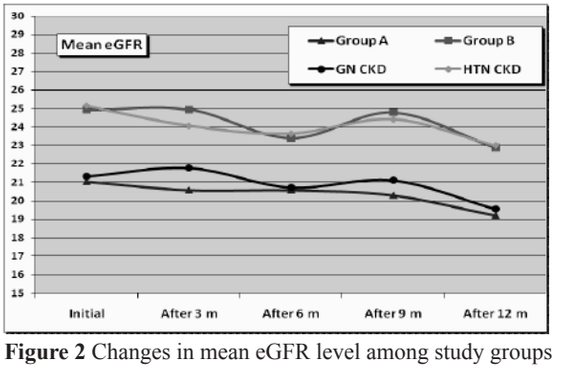

Figure 2 Changes in mean eGFR level among study groups and diagnoses

At the end of 12 months therapy the values of urinary total protein decreased (In percent) were 14.50 ±5.00 in group A, 19.09 ± 7.06 in group B, 18.40 ± 6.19 in GN, CKD and 14.69 ± 6.39 in HTN, CKD.

Table III Statistics of urinary total protein among the study groups and diagnoses (With independent samples t - test significance)

Urinary total protein (gm) Mean ± SD	Study Groups		Diagnoses		Total
	Group A	Group B	GN CKD	HTN CKD	
n	15	15	17	13	30
Initial	1.63 ±1.43	2.24± 1.97	2.08±1.44	1.75± 2.08	1.94±1.72
	p = 0.969^{NS}		p = 0.607^{NS}		
After 3 Months	1.59 ± 1.41	2.03±1.69	1.96±1.33	1.62± 1.82	1.81± 1.54
	p = 0.776^{NS}		p = 0.566^{NS}		
After 6 Months	1.52± 1.33	1.88± 1.51	1.84± 1.26	1.51± 1.62	1.70± 1.41
	p = 0.692^{NS}		p = 0.538^{NS}		
After 9 Months	1.43± 1.22	1.78± 1.40	1.73±1.15	1.44± 1.51	1.60± 1.30
	p = 0.731^{NS}		p = 0.549^{NS}		
After 12 Months	1.35± 1.15	1.71± 1.35	1.65± 1.10	1.38± 1.45	1.53± 1.25
	p = 0.793^{NS}		p = 0.572^{NS}		
Percent Variation	14.50±5.00	19.09±7.06	18.40±6.19	14.69±6.39	16.79±6.45
	p = 2.056^{NS}		p = 0.120^{NS}		

● NS = Not Significant (p>0.05)

Discussion

Studies with ARA II among hypertensive patients with renal impairment have been carried out mostly in diabetic nephropathy.[20-23] Successful outcome found on AHT control, proteinuria and renal disease progression. Stojcevataneva O. et al. showed in a study with patients' stage II – IV CKD followed up for 12-52 months were out of 70 non diabetic patients 34 were male and 36 were female.[24] Their study revealed younger age and higher proteinuria were predictive of CKD progression in nondiabetic patient. Our study revealed similar result where number of female patients were slightly more than male and 60% of study people were younger (Age≤50 years). In our work, the antihypertensive efficacy of a short half-life ARA II, such as losartan has been shown in hypertensive non diabetic and advanced chronic renal disease, followed at a specific outpatient clinic,with similar results (Reduced systolic, diastolic and Pulse blood pressure) to those obtained on intermediate half-life ARA II irbesartanand with similar characteristics, better efficacy on serum uric acid level but worsening of serum potassium level has shown in the former as compared with the latter. In one of the few published studies including a sub group of patients with ACRD of nondiabetic origin and followed up for 3 months: Outcomes similar to ours are obtained for BP control and decrease of proteinuria even when used as mono therapy.[25] Before starting losartan or irbesartan most patients of group A and B received diuretics (Furosemide) irregularly for their symptomatic relief from oedema. This diuretic is also an antihypertensive. Furthermore, ingroup A initial dose of losartan was 50mg daily. It was increased to 100 mg at 3 months for 5 patient and at 6 months for 3 patients.In this group 4 patient were receiving combination of amlodipine 5mg and atenolol 50mg daily before starting losartan but blood pressure was not controlled. In group B initial dose of irbesartan was 150mg daily. It was increased to 300mg at 3 months for 6 patients and at 6 months for 3 patients. In this group 2 patient received amlodipine 5 mg daily and another 2-patient received combination of amlodipine 5 mg and atenolol 50 mg daily before starting irbesartan but blood pressure was not controlled. Kenneth kassler - tabu et al. showed both losartan and Irbesartan slightly increase serum potassium in patients with mild to moderate hypertension.[17] Our result showed the same behaviour of serum potassium by using both drugs in ACRD patients, observing a 26.58% increase with the former as compared with 12.07% increase with the latter. In a study using high doses of candesartan in CKD patient showed no change in baselineserum potassium levels.[26] But our study showed different result that may be due to including patients with advanced CKD where excretion of aldosterone produced by ARA II is low. Analysis of renal failure progression at the end of 12 months therapy revealed no significant difference between losartan and irbesartan (-0.15 and -0.17 ml/min/month respectively) and similar to what has been published by stojceva- Taneva O, et al.[24] Renal disease progression rate of -0.46 ml/min /month of CrCl have been described in patients with nondiabetic chronic renal disease treated with standard antihypertensive medication.[27] This progression rate is reduced down to -0.23 ml/min /month when in a random way patients were

treated with drugs such as captopril or nifedipine.[27] Our result also revealed reduction in progression of renal disease with losartan or irbesartan even in patients with advanced renal disease. As only 2 patient received dialysis therapy before 1st follow up and was excluded from the study. lack of significant difference in renal disease progression between the groups may be related with the low number of sample patients.Antiproteinuric effect of losartan proved in diabetic nephropathy in RENAAL study and similar effect by irbesartan IRMA and IDNT study.[21,20,22] In nondiabetic nephropathy few smaller studies have shown similar effect with Losartan.[28,29] These studies included patients with mild renal failure and the benefit on renal function was independent of blood pressure control.[21,23,28,29] The same effect on reducing proteinuria with losartan as compared with irbesartan observed in our patients. Assessing a group of patients with similar characteristics for three months De Rosa et al. found proteinuria decreased with irbesartan as compared with baseline Values.[25] Another finding in our study was gradual reduction of serum uric acid level with losartan and irbesartan in ACRD patients, observing 30.65% with the former comparing 5.37% with the latter. In our study GN, CKD patients and HTN, CKD patients were almost equal. There was no significant difference of effect of losartan or irbesartan on different parameters e.g., Blood pressure, serum uric acid, serum potassium, proteinuria, creatinine clearance or eGFR.

Limitation

During study period some patients dropped due to refusal,communication difficulties, shifting patient to dialysis unit and sudden death. It was difficult to follow up for long time multiple visits. Only patients from single centre were included in this study. That's is the limitation of this study.

Conclusion

Our result showed that while keeping similar antihypertensive, anti proteinuricefficacy and behaviour in the progression of renal function, losartan reduces serum uric acid at a higher degree than Irbesartan, with significant increase in serum potassium level in patients with advance chronic renal disease of nondiabetic origin. On the otherside irbesartan showed less increase serum potassium but less decrease serum uric acid in comparison with losartan.

Recommendations

- For more accurate result multicentre based study may be done.
- Overcoming the limitations number of sample size can be increased that will give more reliable result.
- In our study result of some parameter may be abnormal due to more advanced CKD rather than the effect of the drugs. So, including more patients at the beginning of advanced CKD, the effect of the drugs can be more accurately evaluated.

Acknowledgement

We are grateful to our patients and their family as well as the doctors, sisters and other staffs of the Nephrology and Medicine Department of CMCH for cooperation in our study.

Contribution of authors

MHRC-Acquisition of data, drafting, analysis & final approval.

MA-Data analysis, drafting & final approval.

BKB-Acquisition of data, drafting & final approval.

MAK-Interpritation of data, drafting & final approval.

MNH-Conception, analysis, critical revision & final approval.

PKD-Design, interpretation of data, critical revision & final approval.

Disclosure

All the authors declared no conflict of interest.

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