ORIGINAL RESEARCH PAPER

Cardiology

A REVISETED STUDY OF ACE, ARB AND COMBINATION OF BOTH IN TREATMENT OF TYPE -2 DIABETIC NEPHROPATHY.

KEY WORDS: Dm-2, Ace-inhibitors, Arb

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ABSTRACT

INTRODUCTION – India known as diabetic capital of the World. Worldwide the leading cause of ESRD in Diabetic Nephropathy.ACE inhibitors are ARBs are used to reduce the proteinuria and to prevent decline in GFR in individual suffering from Type 1 or Type 2 DM. Combined use of both ACE inhibitor and ARB has proven results in decrease of proteinuria. However, there remain concerns over safety of combination use. Further whether there is any additional benefit of combination use on effect on progression of Kidney disease remains questionable. This issue has long been debated and several studies have been conducted to answer this question. This study tries to revisit the same question.

MATERIAL AND METHODS – Study was carried on 150 patients presenting with Type 2 diabetic patient suffering from microalbuminuria at Department of Cardiology, RIMS (A tertiary care hospital) during the period January2018 to June2018. Group A- 50 Pt were replaced with Ramipril, Group -B 50 Pt were placed on Olmesartan and Group C -50 Pt were placed on combination of both. The primary end point was the comparison of change in Urine albumin: creatinine ratio in these groups compared to baseline level.

RESULT– All three groups showed significant decrease in systolic and diastolic blood pressure. All three group show significant decrease in urinary albumin creatinine ratio, maximum in combination group which was statistically significant with respect to other group. However, it is to be noted here that the combination therapy was able to control blood pressure levels most effectively and the higher decrease in albumin: creatinine ratio may be a function of better blood pressure control rather than more complete blockade of the Renin Angiotensin System. Minor increase in potassium and creatinine levels were seen in some patients but it was neither statistically significant nor necessitated discontinuation of medication.

CONCLUSION- The results of this study support the theory that the RAS has a role in progression of renal disease and a more complete blockade of RAS by ACE-1 and ARB results in better control of blood pressure and decreases albumin loss in urine.

INTRODUCTION

Diabetic nephropathy is a major cause of morbidity and mortality for persons with Type2Diabetes mellitus. Worldwide diabetes is one of the leading cause of ESRD.Evidence suggests that early treatment delays or prevents the onset of diabetic nephropathy.In Diabetes microalbuminuria should be detected at an early stage, so that effective therapies can be instituted to prevent the progression of diabetic nephropathy. Either ACE inhibitor or ARB should be used to reduce the albuminuria and the associated decline in GFR.Most studies believe that the two classes of drugs are equivalent in the patient with diabetes. Here the question is whether the combination of these two types of drugs is more effective than either drug alone. Intensive glycaemic control therapy designed to achieve better glycaemic control is able to attenuate the development of nephropathy as assessed by urinary albumin excretion. However other factors are also involved. Interruption of Renin angiotensin system is an excellent, not only for reducing BP but also for correcting many of cellular, biochemical, hemodynamic and structural abnormalities seen in diabetic kidney.This topic has been chosen with an aim to assess the efficacy of combined treatment of ACE inhibitor and ARB ,and monotherapy of each drug at its maximum dose, in patients with type 2 Diabetic nephropathy.

MATERIAL AND METHODS

150 Patients visited in Cardiology Department of Rajendra Institute of Medical Sciences, Ranchi with diagnosis of Type 2 DM suffering from microalbuminuria were selected for the study.

INCLUSION CRITERIA

1. Confirmed diagnosis of Type 2 Diabetes Mellitus
2. Age limit of 40-70 years.
3. The diagnosis of microalbuminuria.

MATERIALS AND METHODS

1. All patients were randomized into three groups, Group A, B and C using a computer program to avoid bias:
2. GROUP-A-50 patients were placed on Ramipril with starting dose of 1.25mg increasing up to 10 mg.
3. GROUP-B-50 patients were placed on Olmesartan with starting dose of 20 mg increasing up to 40 mg.
4. GROUP-C 50 Patients were placed on both Olmesartan(20mg) and Ramipril(1.25mg) gradually increasing.
5. All patients attended the hospital for 7 study visits,4 weeks before randomization, at randomization[0]& 4,8,12,18&24 weeks to study the clinical, hemodynamic, biochemical and response.The primary end point was the comparison of change in urine albumin: creatinine ratio in three groups as compared to baseline levels.
6. Urinary albumin:creatinine ratio of early morning voided urine sample was used.
7. Glycated haemoglobin was measured by spectrophot ometric method.
8. Sitting blood pressure was measured three times with an interval of 15 minute and mean was calculated.
9. All patients were subjected to routine examination fasting and postprandial blood sugar. Complete haemogram full biochemical profile and lipid profile.

EXCLUSION CRITERIA

1. Overt nephropathy [serum creatinine>1.5mg/dl, urinary albumin creatinine ratio >25 mg/mmol],sepsis, urinary tract infection, recent surgery, coronary disease, stroke chronic liver disease, severe hypertension,heart failure, pregnancy and alcohol abuse.
2. All patients gave their informed consent before being included in the study.

STATISTICAL ANALYSIS-

Observational value was represented in s (%) and mean $\pm$ standard deviation, data were entered into Microsoft Excel Worksheet and analyzed using appropriate test.

RESULTS

Out of the 150 patients, 50 were randomized to each group. 28 patients did not turn up for regular follow up and had to be excluded from the study.30 patients were excluded due to adverse effect (20 had dry cough,1had angioedema and 1 had skin rash) from study. Effect on mean systolic blood pressure in the three study groups at follow up visits shown in Table 1.Tables 2 and3 shows the statistical significance decrease in systolic blood pressure in each group. Table 4 shows effect on mean diastolic blood pressure in the three study groups.Tables5, 6 and 7show the effect on mean with Statistical significance of decrease in Urinary Albumin Creatinine Ratio in each group at different pair intervals.

Table 1

Effect on mean systolic blood pressure in the three study groups at follow up visits.			
Study	Initial (mean±SD) mmHg	12TH WEEK (mean±SD) mmHg	24TH WEEK (mean±SD) mmHg
Ramipril	145.68±12.21	140.32±12.01	138.19±10.74
Olmesartan	142.60±11.97	137.47±11.24	136.33±11.18
Combination	147.55±10.17	137.29±6.60	135.23±8.19

Table 2

Statistical significance of decrease in systolic blood pressure in each group at different pair intervals				
Study	0-12 weeks		0:24 weeks	
	Mean Difference	p value	Mean Difference	p value
Ramipril	5.35mmHg	<0.01	7.48 mmHg	<0.01
Olmesartan	5.13mmHg	<0.01	6.27 mmHg	<0.01
Combination	10.26mmHg	<0.01	12.32mmHg	<0.01

Table 3

Statistical significance of the decrease in systolic blood pressure in different study groups when compared with each other at 24 weeks.			
	RAMIPRIL: OLMESARTAN	RAMIPRIL: COMBINATION	OLMESARTAN: COMBINATION
Mean difference	1.33 mmHg	-5.48 mmHg	-6.80 mmHg
P value	0.3422	<0.01	<0.01

Table 4

Effect on mean diastolic blood pressure in the three study groups at follow up visits.			
Study	Initial (mean±SD) mmHg	12 TH WEEK (mean±SD) mmHg	24TH WEEK (mean±SD) mmHg
Ramipril	85.03±7.26	79.55±7.55	79.68±6.93
Olmesartan	80.80±6.49	77.40±6.37	77.53 ±6.98
Combination	84.97±5.77	82.13±5.63	76.77±5.43

Table 5

Effect on mean Urinary Albumin Creatinine Ratio in the three study groups at follow up visits.			
Study	Initial (mean±SD) mg/mmol	12 TH WEEK (mean±SD) mg/mmol	24TH WEEK (mean±SD) mg/mmol
Ramipril	16.039±5769	15.355±5.681	14.655±5.615
Olmesartan	14.533±5.340	13.783±5.301	13.057±5.276
Combination	15.142±4.693	12839±4.825	9.106±4.727

Table 6

Statistical significance of decrease in Urinary Albumin CreatinineRatio in each group at different pair intervals				
Study	0-12 weeks	0-24 weeks		
	Mean difference	p value	Mean difference	p value
Ramipril	0.684	<0.01	1.384	<0.01
Olmesartan	0.75	<0.01	1.477	<0.01
Combination	2.303	<0.01	4.174	<0.01

Table 7

Statistical significance of the decrease Urinary Albumin Creatinine Ratio in different study groups when compared with each other at 24weeks.			
	RAMIPRIL: OLMESARTAN	RAMIPRIL: COMBINATION	OLMESARTAN. COMBINATION
Mean	-0.097	-2.79	-2.733
value	0.3185	<0.01	<0.01

DISCUSSION

This study was carried out to compare the effects of Ramipril, Olmesartan and combination of both in Patients of T2DM with incipient nephropathy. The studywas designed to compare the clinical,hemodynamic, biochemical changes and progression of diabetic nephropathy in each group. Several studies have been done on similar issues in the past. Most of these studies have been done in western countries. Some studies have been done in India also.In this study all three groups showed significant decrease in systolic and diastolic blood pressures.Maximum decrease was seen in the combination group which was significant with respect to decrease in the other two groups[p<0.01].The urinary albumin creatinine ratio decreased by a mean of 4.174 mg/mmol in case of combination group,whereas it decreased by 1.384 mg/mmol in case of ramipril and by 1.477mg/mmol in case of Olmesartan. All these were significant reductions in comparison with initial values in each group[p<0.01]. The study thus confirms the effectiveness of RAS blockade in halting the progression of Type 2 Diabetic Nephropathy. The study also confirms that the dual blockade of the renin-angiotensin system, both at the level of ACE and at the level of A-2 receptor is associated with more effective reduction in proteinuria than observed with single agent. This result is comparable with the CALM; study 2000,which also showed reduction in blood pressure and urinary albumin: creatinine ratio after12 weeks of treatment from baseline with candesartan and lisinopril.

CONCLUSION

This study was designed to compare the effect of Ramipril, Olmesartan and combination of both in cases of type 2 Diabetes Mellitus with microalbuminuria. All the three groups showed significant decrease in systolic and diastolic blood pressure. Maximum decreasewas seen in the combination group. All three groups showed significant decrease in urinary albumin creatinine ratio. Maximum decrease was seen in the combination group.This difference was significant with respect to decrease in the other two groups.The results of this study support the theory that the RAS has a role in progression of renal disease and a more complete blockade of RAS by ACE-1 and ARB results in better control of blood pressure and decreases albumin loss in urine. This study however, can't determine if these effects on urinary albumin excretion are due to more effective reduction in blood pressure or to more complete blockade of the renin angiotensin system, and thus this need further analysis.

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