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IJPBS |Volume 4| Issue 2|APR-JUN|2014|122-127

Research Article
Biological Sciences

A COMPARATIVE STUDY TO EVALUATE THE EFFECT OF RAMIPRIL AND TELMISARTAN ON THE COMPONENTS OF METABOLIC SYNDROME IN CHRONIC KIDNEY DISEASE PATIENTS

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ABSTRACT

Background: *Metabolic syndrome (MetS) a Multifactorial disorder increases the risk of chronic non-communicable diseases, thereby raising the morbidity and mortality rates. In this situation halting the progression of MetS and its complications have great impact on health statistics which made us to carry out this study.* ***Objectives:*** *To assess and compare the effect of Ramipril and Telmisartan in modulating the components of MetS i.e., Waist circumference (WCf), blood pressure, Fasting blood sugar (FBS), Insulin resistance (IR) and lipid profile before and after the treatment period.* ***Materials and methods:*** *The study was done in Nephrology outpatient department, NIMS after approval of institutional ethics committee for a study period of 24 weeks. Patients (N=31), who met with inclusion/exclusion criteria, assigned randomly into one of the study groups (Ramipril-5mg (n=16)/Telmisartan-40mg (n=15) given orally). The parameters of MetS were assessed before and after the study period and statistical analysis done by t-test.* ***Results:*** *In the ramipril group we observed significant difference in weight (p=0.002), body mass index (BMI, p=0.02), systolic blood pressure (SBP, p=0.0002), Diastolic blood pressure (DBP, p=0.0008) and triglyceride (p=0.02) after 24weeks. In the telmisartan group significant difference noted in weight (p=0.03), WCf(p=0.006), SBP(p=0.0003), DBP(p=0.0002), FBS(p=0.03), high density lipoproteins(p=0.003), TG(p=0.02) after 24 weeks. For all the parameters assessed, we could not find any significant difference in between the groups.* ***Conclusion:*** *Ramipril and Telmisartan are equally efficacious drugs in decreasing the weight, blood pressure and altering lipid profile. There was no significant effect on insulin resistance with both drugs. Further studies with larger sample size are needed to know the effect on MetS components.*

KEY WORDS

HOMA-IR, Insulin Resistance, Obesity.

INTRODUCTION

Metabolic syndrome (MetS) a global burden, also called insulin resistance syndrome or syndrome X, is a cluster of risk factors such as abdominal obesity, atherogenic dyslipidaemia, raised blood pressure, insulin resistance, prothrombotic and proinflammatory states [1]. Different definitions proposed by different organizations with different cut-off parameters and accordingly the prevalence varies [2, 3]. Global prevalence of MetS is rising due to increasing obesity and change in lifestyle posing a major problem to the individual and the government. The prevalence among the men varies from 8% in India to 24% in United States and among the women it varies from 7% in France to 46% in India[4]. MetS is catching the attention of researchers due to its strong

association with the non communicable diseases (NCD) i.e., cardiovascular disease (CVD), type 2 Diabetes mellitus (T2DM), cerebrovascular & chronic kidney diseases (CKD). The progression of MetS can be prevented by maintaining the components of MetS within normal range. Though International Diabetes federation (IDF) recommends the use of Angiotensin converting enzyme inhibitors (ACEIs) and Angiotensin receptor blockers (ARBs) in the hypertension treatment in patients of MetS, but ultimately states that any antihypertensive drug can be used[5]. Moreover ACEIs and ARBs are known for reno-protection and also retard the progression of end stage renal disease (ESRD). Hence the present study was designed to comapare the effect of ACEI (Tab.Ramipril) and ARB (Tab.Telmisartan) on the components of MetS in chronic kidney disease metabolic syndrome patients.

AIMS AND OBJECTIVES

To evaluate and compare the effect of Ramipril and Telmisartan on the individual components of Metabolic Syndrome after the treatment period of 24 weeks.

MATERIALS AND METHODS

It was a 24 week prospective open label two arm parallel group study done in the outpatient department of nephrology at Nizam's Institute of Medical Sciences, Hyderabad, after the approval of institutional ethical committee. Out of the 40 recruited patients who met with criteria, 9 patients lost follow up. Patients were enrolled randomly into either of the study group (Ramipril-5mg/ Telmisartan-40mg) after taking the written informed consent and the wash out period of two weeks with Tab. Amlodipine (calcium channel blocker). Criteria of including the patients was either sex with age between 25 - 65yrs, Blood pressure ≥130/85 mmHG and <160/100 mmHg, Serum Creatinine < 3mg/dl, waist circumference ≥90cms in men and ≥80cms for women. Patients with chronic liver disease, chronic renal failure with serum Creatinine > 3mg/dl, congestive cardiac failure, life threatening arrhythmias, cardiomyopathy, coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease, haemoglobinopathies, hemophilia, active auto-immune diseases, severe pre-existing psychiatric disease and narcolepsy were excluded. In the remaining 31 patients, 16 (M - 11, F-5) were in Ramipril group and 15 (M-13, F - 2) in Telmisartan group. The drugs were given once a day orally for a period of 24 weeks and the doses were Ramipril - 5mg (Tab. Ramace from AstraZeneca) and Telmisartan - 40mg (Tab.Telma 40 mg from Glenmark pharma). During the first visit details of the demographic data, physical and clinical examination was recorded. The parameters like waist circumference (WCf), Hip circumference, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Laboratory tests i.e., FBS, Fasting Insulin(FI), high density lipoproteins (HDL), triglycerides (TG), Liver function and renal function tests were done. Blood samples were collected after 12hrs of overnight fasting. The estimate of Insulin Resistance (IR) index was calculated based on Homeostasis Model Assessment – Insulin Resistance (HOMA-IR) with the formula [6]:

IR = Fasting Serum Insulin (µU/ml) × Fasting Plasma Glucose (mg/dl) ÷ 405

At the end of 24 weeks study period we have reassessed the weight, WCf, Hip circumference, blood pressure, FBS, FI, IR, lipid profile, liver function tests, renal function tests and the patient compliance in both the study groups.

STATISTICAL ANALYSIS

Data was spread in Microsoft Excel sheet and analysed using Excel (2010 version) statistical tool. Mean ± SD was calculated for all the parameters and statistical analysis was done by paired t-test for intra-group comparison and unpaired t-test for Inter-group comparison (between Ramipril and Telmisartan). P<0.05 was considered as significant.

RESULTS

In our study there was no statistically significant difference in the demographic parameters i.e., age, weight and height in between the two groups prior to the start of study. After the treatment period of 24weeks with ramipril, we observed significant difference in parameters like weight (p=0.002), BMI (p=0.002), SBP (p=0.0002), DBP (p=0.0008), and in TG (p=0.02). Significant difference was not observed in the rest of the parameters i.e., WCf, HCf, W/H ratio, FBS, FI, IR and HDL after the treatment period. After the treatment with telmisartan for 24 weeks period, significant difference noted in parameters like weight (p=0.03), WCf (p=0.006), SBP (p=0.0003), DBP (p=0.0002), FBS (p=0.03),HDL (p=0.003) and in TG (p=0.02) but no significant difference was observed in parameters like HCf, W/H ratio, BMI, FI and IR. The other parameters like blood urea (Bl.Ur), Serum Creatinine (S.Cr), serum electrolytes (Sodium-Na^+, Potassium-K^+, Chloride-Cl^-), liver function tests were also assessed [**Table 1, Graph 1**]. Mean difference of all the parameters after the treatment period was calculated and expressed in Mean ±SD. When inter-group comparison was done by unpaired t-test, no significant difference was observed between ramipril and telmisartan [**Table 2**].

Table 1: Assessment of parameters of MetS: Pre and post treatment of Ramipril and Telmisartan expressed in Mean ± SD[a] and p-value

Para-meter	Ramipril (n=16)			Telmisartan (n=15)		
	Pre (Mean ± SD)	Post (Mean ± SD)	p-value	Pre (Mean ± SD)	Post (Mean ± SD)	p-value
Wt	67.11±13.21	65.69±13.01	0.002*	77.6±15.97	76.87±16.36	0.03*
WCf	89.38±8.4	88.53±8.42	0.25	95.6±9.65	94.6±9.77	0.006*
HCf	95.47±7.5	95.38±6.77	0.84	98.53±7.0	98.07±7.1	0.08
W/H	0.94±0.03	0.93±0.04	0.3	0.97±0.05	0.96±0.05	0.16
BMI	24.33±3.59	23.8±3.5	0.002*	27.14±4.56	26.03±4.53	0.08
SBP	150±23.18	130.75±26.9	0.0002*	146.27±20.8	123.87±8.09	0.0003*
DBP	98.19±16.48	87.25±13.34	0.0008*	91.87±11.21	82.0±4.78	0.0002*
FBS	100.25±22.61	92.75±11.87	0.07	92.4±10.2	86.87±9.0	0.03*
FI	12.72±5.47	12.18±5.17	0.48	8.49±3.7	8.49±5.5	1
IR	3.2±1.51	2.89±1.4	0.09	1.99±1.0	1.92±1.45	0.52
HDL	38.19±4.4	39.44±6.6	0.43	37.87±8.03	41.06±8.01	0.003
TG	141.38±54.13	117.38±34.68	0.02*	150.33±47.46	127.13±29.34	0.02
Bl.Ur	23.43±7.18	20.4±6.54	0.23	38.5±20.36	38.33±18.5	1.0
S.Cr	1.1±0.2	1.06±0.25	0.48	1.89±0.88	2.43±1.32	0.08
Na^+	140.88±1.36	137±2.77	0.07	141.63±4.79	140±5.13	0.09
K^+	4.42±0.60	4.72±0.43	0.52	4.41±0.53	4.46±0.78	0.92
Cl^-	101.4±2.7	99±1	0.08	104.14±4.08	104.14±6.47	0.94

[a]Standard deviation, *statistically significant p-value

Graph 1: Pre and Post comparison of the MetS components after 24 weeks treatment period with Ramipril / Telmisartan

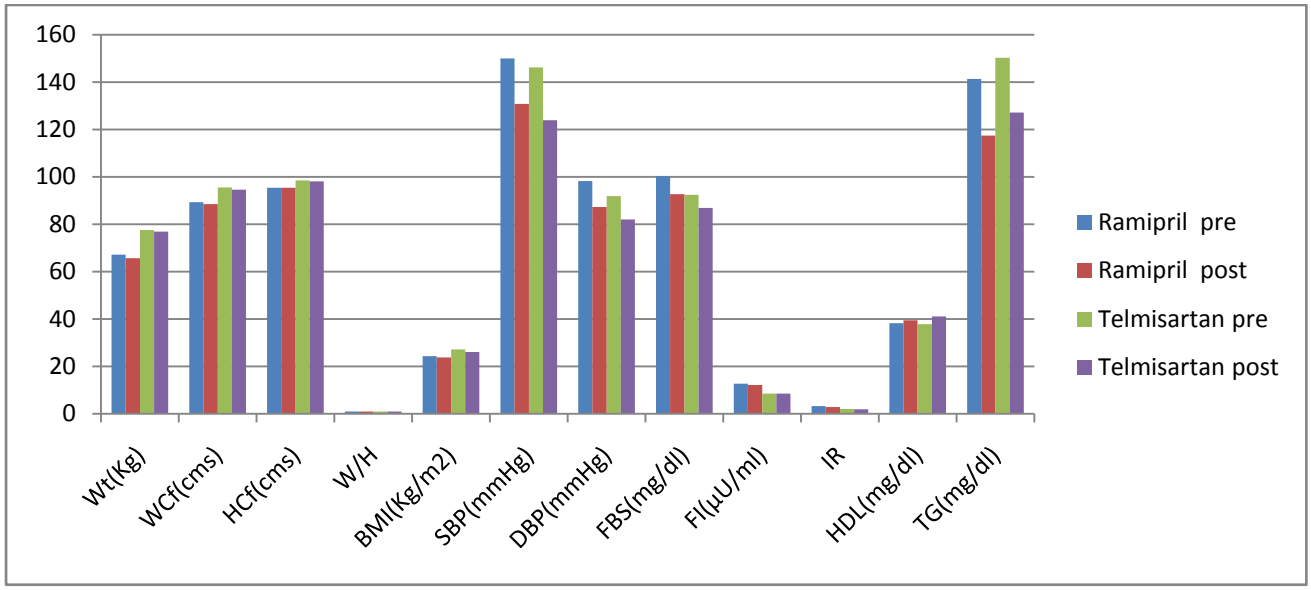

Table 2: Intergroup comparison of Ramipril and Telmisartan

Parameter	Ramipril Difference Mean ± SD	Telmisartan Difference Mean ± SD	p-value in between groups
Wt	1.24±2.04	0.73±1.21	0.41
WCf	0.59±3.65	1±1.2	0.68
HCf	0.09±1.77	0.47±0.97	0.48
W/H	0.008±0.03	0.01±0.01	0.77
BMI	0.53±0.55	1.11±2.32	0.34
SBP	19.25±16.04	22.4±18.03	0.61
DBP	10.94±10.45	9.87±7.52	0.75
FBS	7.5±15.21	5.53±8.98	0.67
FI	0.54±3.0	0.01±4.75	0.71
IR	0.31±0.69	0.07±1.28	0.52
HDL	1.25±6.2	3.73±3.95	0.2
TG	24±37.5	23.2±35.17	0.95

DISCUSSION

Indian health statistics-2010, estimated that NCDs accounts for nearly 53% of total deaths, out of which death from CVD's is 24%, DM is 2%, other NCDs is 10%. NCDs are prevalent across all the socioeconomic classes. Among the deaths from CVDs 61% are due to the modifiable risk factors, which include use of tobacco / alcohol, low intake of fruits/vegetables, decreased physical inactivity, overweight and obesity, high blood pressure / blood glucose / blood cholesterol. These risk factors are nothing but the components of MetS, hence urgent measures are to be taken to identify the patients with MetS and prevent further progression of the disease. If we could decrease the prevalence & progression of the MetS, the morbidity and mortality rate from all the non communicable diseases also comes down. Approach towards a MetS patient till now include the

pharmacotherapy of individual component i.e., with anti-hypertensives, hypolipidaemic drugs, anti diabetic drugs, physical activity etc. No single agent is available to treat all the components of MetS. Hence in our study, we have evaluated the effects of ACEI's and ARB's on the components of MetS.

Many studies suggested that Angiotensin II may promote impaired glucose metabolism through its effects on insulin signaling pathways, tissue blood flow, oxidative stress, sympathetic activity and adipogenesis[7]. Hence the drugs blocking the Angiotensin II have to improve insulin sensitivity and decrease obesity / lipid levels, but this is not happening with all the ACEIs or ARBs. Here the question rises, whether the interruption of the renin-angiotensin system per se expected to lead the improvement in carbohydrate and lipid metabolism or not. Recent studies have indicated that improvement of insulin resistance by ACE inhibitors is largely mediated through increase in bradykinin levels, nitric oxide and translocation of GLUT4 glucose transporter [8]. In case of ARB's like Telmisartan which is distinct from other ARB's in having unique chemical structure(non tetrazole derivative with single carboxylic acid group) similar to insulin sensitizers i.e., Pioglitazone. Telmisartan is a partial agonist of peroxisome proliferator-activated receptor –gamma (PPARγ) and also called Selective PPARγ Modulators (SPPARM)[9]. PPARγ is the member of nuclear hormone receptor super family and functions as transcription factor that regulates the expression of multiple genes involved in carbohydrate, lipid metabolism and inflammation. Hence the ligands for PPARγ like Telmisartan can decrease the risk for atherosclerosis by improving insulin sensitivity, reduce triglyceride levels and decrease visceral fat mass in patients with T2DM and MetS, thus can be used not only in the treatment of hypertension but also for the prevention of metabolic syndrome.

Our study findings are comparable with the above conclusions as we noted significant reduction in weight, blood pressure and TG in both groups indicating that these anti-hypertensive drugs i.e., ramipril and telmisartan have significant effect in reducing the obesity and lowering TG levels. The other aspect in our study was to find the effect of these drugs on FBS, FI and IR and we did not observe significant change in FI and IR in both the groups, except a significant decrease in FBS in telmisartan group. Even though significant difference was not observed, there was decrease in the mean value compared to the pretreatment period. The post treatment findings of our study with Telmisartan on IR were comparable to the studies done by Bahadir et al[10], which is a 8 week study between Telmisartan-80mg and Losartan-50mg (N=42) and Derosa G et al[11] study between Telmisartan-40mg and Eprosartan with treatment period of 1 year. One of the possible reasons for not having the significant effect on IR might be the use of relatively low dose of telmisartan i.e., 40 mg once daily might be insufficient to act as a PPARγ agonist, for the full manifestation of hypoglycemic effects. Significant effect of Telmisartan on IR at higher dose of 80 mg was supported in studies done by S. Sarac et al [12] (Telmisartan-80mg,n=70 and Valsartan-160mg,n=50 for 6 months) and Cristiana Vitale et al[13] (Telmisartan-80 mg and Losartan-50 mg for 3 months, N=40).

When intergroup comparison was done there was no significant difference i.e., we could not find any superiority of Telmisartan over Ramipril and the findings were similar to other studies like ONTARGET [14]. All the above studies were done in patients with hypertension, metabolic syndrome, but studies on CKD with hypertension and MetS were limited though many studies were done on ACEIs and ARBs in relation to CKD. Hence in this study, when we evaluated the ramipril and telmisartan in CKD MetS patients, we observed these drugs prevent the progression of NCDs by decreasing obesity and hyperlipidaemia apart from CKD where they have proven efficacy.

CONCLUSION

From the present study we have concluded that both Ramipril and Telmisartan are equally efficacious drugs in decreasing the hypertension. Apart from antihypertensive action, both drugs were equally effective in decreasing the weight and altering the lipid profile hence were cardio protective. As we could not observe significant effect on FI, IR further studies with larger sample size and varying doses are

needed to establish their effect in halting the progression of IR to Type 2 Diabetes Mellitus.

ACKNOWLEDGEMENT

I express my heartfelt thanks to the Dept. of pharmacology- Gandhi Medical College, Dept. of Nephrology-NIMS, my family and the patients who extended their arms in completing the study.

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