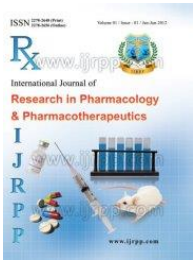
International Journal of Research in Pharmacology & Pharmacotherapeutics



ISSN Print: 2278-2648 ***IJRPP |Vol.8 | Issue 3 | Jul - Sep - 2019***
ISSN Online: 2278-2656 ***Journal Home page: www.ijrpp.com***

Research article ***Open Access***

Comparative study on efficacy and safety of Rosuvastatin v/s Atorvastatin in patients with metabolic syndrome- a prospective observational study

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ABSTRACT

Background

Metabolic Syndrome is a constellation of cardio metabolic abnormalities such as central obesity, dyslipidemia, hyperglycemia, hypertension, proinflammatory and prothrombotic state. Dyslipidemia is one of the important components of this syndrome and also important risk factor for cardiovascular disease. Statins are used as first line drugs for dyslipidemia but right now several drugs are available in Indian market and it is difficult for medical practitioners to select a suitable one among them. This is a study to evaluate the efficacy and safety of most commonly used atorvastatin with rosuvastatin in patients with metabolic syndrome.

Objectives

To compare the efficacy and safety of Rosuvastatin and Atorvastatin in patients with metabolic syndrome.

Methods

A total of 60 subjects diagnosed with Metabolic syndrome were included in the study. They were randomized into two groups, the first group received, Rosuvastatin 10mg and second group received Atorvastatin 10 mg for 6 weeks. Lipid profile was evaluated for efficacy; liver function tests (LFT) and serum creatine for safety. Adverse effects were evaluated based on symptomatology and laboratory parameters.

Results

Both the groups showed significant improvement in lipid profile, seen by reduction in LDL, Triglycerides, total cholesterol and increase in HDL levels compared to baseline values ($p<0.001$). Intergroup comparison showed that 10mg of Rosuvastatin was better in providing a favourable lipid profile compared to 10mg of Atorvastatin. Changes in LFT and serum creatine were not significant statistically both within and between the groups.

Conclusion

Rosuvastatin was found to be better than atorvastatin in providing a favourable lipid profile for patients with metabolic syndrome and both the drugs were well tolerated and safe.

Keywords: Metabolic syndrome, dyslipidemia, atorvastatin, rosuvastatin.

INTRODUCTION

The term metabolic syndrome [METS] denotes a clustering of emerging risk factors for type 2 diabetes and cardiovascular disease. It consists of constellation of cardio metabolic abnormalities such as central obesity, dyslipidemia, hyperglycemia, hypertension, proinflammatory and prothrombotic state.[1,2]

With globalization and industrialization there have been changes in lifestyle leading to increasing incidence and prevalence of non-communicable disorders like obesity, diabetes, hypercholesterolemia, hypertension throughout the world. It is expected that by 2020 in developing countries, non-communicable disease will account for 69% of all deaths, with cardiovascular diseases in the lead[3]. In parallel to this there is rapid growth in the prevalence of metabolic syndrome, thus is being considered as a major public health problem and a subject of considerable interest [4,5]. The prevalence of metabolic syndrome varies around the world, according to age, ethnicity and diagnostic criteria used. Clustering of these risk factors was recognised more than 80 years ago but modern concept of metabolic syndrome began when Reaven brought out a framework which linked unrelated biological events. [1,6]

The concept of metabolic syndrome focuses on complex multifactorial health problems but still WHO [World health organization] considers it to be a premorbid condition rather than a diagnosis. Metabolic syndrome especially in the presence of high LDL-C [Low density lipoprotein- Cholesterol] levels is known to increase the risk of cardiovascular mortality as it may lead to complications like myocardial infarction, stroke, peripheral vascular disease. [1,6,7]

The management of metabolic syndrome consists of weight reduction, dietary fat restriction, increased physical activity, adequate control of blood pressure and blood glucose levels, along with the use of hypolipidemic drugs to maintain favourable lipid profile. [1]

There are cost effective strategies to prevent and control constituents of metabolic syndrome but non communicable disease programmes are underfunded both at national and global levels and prevention is not included in current millennium development goals. [8] But as the condition is increasing dramatically there is a need for an action to prevent and control it thus preventing the development of further complications. Life style modifications such as dietary changes, increased physical activity are crucial for prevention.[9] Pharmacological interventions like metformin and statins target the physiological mechanisms involved in METS and are currently in practice.[5]

Dyslipidemia is one of the component of METS and also an important risk factor for cardiovascular diseases [1]. Among the various hypolipidemic drugs, statins provide a favorable lipid profile and are most effective and best tolerated for treating dyslipidemia [10]. So they are presently used as first line agents in the treatment of dyslipidemia. [7]

Statins also called as HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors have been developed as lipid-lowering drugs by inhibiting the rate limiting step in cholesterol synthesis and are well established to reduce serum cholesterol levels and morbidity and mortality from coronary artery disease because of their pleiotropic effects.[11]

The activity of HMG-CoA reductase limits the rate of synthesis not only of cholesterol but also of a range of other molecules involved in functions such as cellular respiration and cell-cell recognition. Therefore statins, as inhibitors of this enzyme, might modify constituents of the vascular milieu other than LDL cholesterol.[12]

Statins also have “pleiotropic” effects such as reducing oxidative stress and modulating inflammatory responses and these effects may improve other risk factors associated with metabolic syndrome. [13]

Atorvastatin and Rosuvastatin are entirely synthetic compounds containing heptanoic acid side chain that forms structural analogue of HMG CoA intermediate. They competitively inhibit HMG-CoA Reductase which catalyzes the rate limiting step in cholesterol synthesis; HMG COA to mevalonate. This decreases hepatic cholesterol synthesis and leads to an up-regulation of hepatic LDL receptors with subsequent increased LDL-C uptake and decreased plasma LDL-C levels.[14,15,10]

There are several statins available in Indian market like Atorvastatin, Simvastatin, Pravastatin, Pitavastatin, Fluvastatin, Rosuvastatin etc. [16] Atorvastatin is the most widely used statin. Rosuvastatin a newer drug, has been proven in

various studies to be the most potent and well tolerated among all statins in hypercholesterolemia[17,14, 15]. Many studies suggest that efficacy and safety of various statins varies considerably and it is difficult for medical practitioners to select suitable statins for dyslipidemic patients.[16] So it is an attempt to compare the efficacy and safety of Rosuvastatin with most commonly used drug, Atorvastatin, in patients with metabolic syndrome.

OBJECTIVE

- ✓ To compare the efficacy and safety of Rosuvastatin and Atorvastatin in patients with metabolic syndrome.

MATERIALS AND METHODS

- **Study design**: Prospective open label observational study
- **Study period**: March 2013- March 2014.
- **Source of data and study population**: The study was carried out in subjects who met inclusion criteria of metabolic syndrome and were selected from Bapuji hospital and Chigateri General Hospital, Davangere. (Both the hospitals are attached to teaching institute, JJM Medical College, Davangere)

Inclusion Criteria

- Patients selected include both males and females >18 years of age.
- Patients satisfying National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) criteria of metabolic syndrome which requires at least 3 of the following.
  a. Waist circumference : Men - ≥ 102 cm
  Women- ≥ 88 cm
  b. b) Triglyceride levels : ≥ 150 mg/dl
  c. c) HDL levels : Men ≤ 40 mg/dl
  Women ≤ 50 mg /dl
  d. d) BP ≥ 130 systolic or ≥ 85 diastolic or on treatment
  e. e) FBS ≥ 100 mg /dl or with type 2 diabetes mellitus

Exclusion Criteria

- Patients with h/o use of lipid lowering agents with in past six months.
- Patients with acute liver disease or hepatic failure.
- Pregnant and lactating women.
- Patients with h/o serious or hypersensitivity reactions to statins.
- Patients with documented h/o coronary artery disease or other atherosclerotic disease.
- Patients with uncontrolled hypothyroidism or hypertension.
- Patients of familial hypercholesterolemia.
- Patients taking other class of hypolipidemic drugs (fibrates, niacin) and taking other cardiac drugs like Warfarin, Verapamil and Amiodarone.
- Patients taking Immunosupressants, Azole antifungal agents, Protease inhibitors.

Study subjects and randomization

Based on inclusion and exclusion criteria a total of 60 patients were selected for the present study. They were randomized in 1:1 ratio, into two groups of 30 patients in each group (n=30). First group received Rosuvastatin 10mg as test drug whereas second group was received Atorvastatin 10 mg as standard drug. The patients were advised to take medications once daily at bed time and follow normal regular diet for 6 weeks.

Study procedure

Each of the study subject voluntarily gave an informed written consent after being explained in their own language about the study procedure, drugs used and investigations done. The study was approved by the ethical and research committee of JJM Medical college, Davangere to use human subjects in the research study.

The subjects were enquired for basic details and about other questions mentioned in the proforma. Anthropometric measurements and general physical examination was done before initiation of the therapy. Blood samples were collected before the randomization, with the patient fasting for at least 12 hours. Investigations like fasting lipid profile, fasting blood glucose, liver function tests and creatine kinase was done before initiation of treatment.

During the follow up after 6 weeks, subjects were enquired for side effects related to statins, again anthropometric measurements and general physical examination was done. Fasting lipid profile, fasting blood glucose, liver function tests and creatine kinase were repeated after 12 hours of fasting.

Statistical analysis

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. After collecting the data, intragroup comparisons was made by Paired T- Test and intergroup comparison was made by Unpaired T-Test.

A 'p' value of ≤0.001 was considered very highly significant, a value of ≤0.01 was highly significant, a value of ≤0.05 was significant and a value > 0.05 was insignificant.

RESULTS

A total of 60 patients who were fulfilling the inclusion criteria were randomized in two treatment groups and the baseline demographic parameters were comparable in both the groups. (Table-1)

Table 1: Comparison of age wise and gender distribution between groups

Demographic variables		GROUP-1 ROSUVASTATIN N=30	GROUP-2 ATORVASTATINN=30
Mean age & SD (in yrs)		54.3 ± 9.52	52.2 ± 10.44
Age (In years)	50 & below	14	17
	51 & above	16	13
Sex	Male	17	16
	Female	13	14

Efficacy Parameters

Comparing the both the treatment groups Rosuvastatin and Atorvastatin there were no clinically significant changes in the anthropometric values (Weight, BMI, Waist circumference) before and after treatment. (Table-2)

Table 2: Comparison of anthropometric measurements between group 1 and group 2

Clinical Variables	GROUP-1 (ROSUVASTATIN) Difference between before & After N=30		GROUP-2 (ATORVASTATIN) Difference between Before & After N=30		Unpaired t test f=28, p values
	Mean	S D	Mean	S.D	
Height (in mts)	0.002	0.12	0.002	0.12	0
Weight(in Kgs)	0.06	0.43	0.1	0.3	0.34, NS
Weight(in Kgs)	0.06	0.43	0.1	0.3	0.34, NS
BMI	0.01	0.12	0.006	0.05	0.26, NS
Waist Circumference (in cms)	0.03	0.12	0.1	0.54	0.39, NS

LIPID PROFILE

Rosuvastatin 10mg increased HDL-C levels to greater levels than Atorvastatin 10mg (mean change from baseline was 15.4 mg/dl and 6.47 mg/dl respectively), which was statistically significant (P <0.002). Rosuvastatin was more effective in reduction of TC, TG and LDL in comparison to Atorvastatin and was statistically significant. (Table-3, fig -1)

Table 3: Comparison of lipid parameters between group 1 and group 2

Clinical Variable Lipid profile	GROUP-1 (ROSUVASTATIN) Difference between before & After N=30		GROUP-2 (ATORVASTATIN) Difference between Before & After N=30		Statistical Analysis unpaired t test df=28 p values
	Mean (in mg/dl)	Std Deviation	Mean (in mg/dl)	Std Deviation	
Total Cholesterol	64.87	47.49	38.43	36.45	2.42, P<0.01
LDL – C	41.83	30.91	23.56	29.99	2.32, P<0.02
HDL – C	-15.4	5.39	-6.47	4.41	7.02, P<0.001
Triglycerides	82.3	65.68	40.26	44.88	2.89, P<0.005

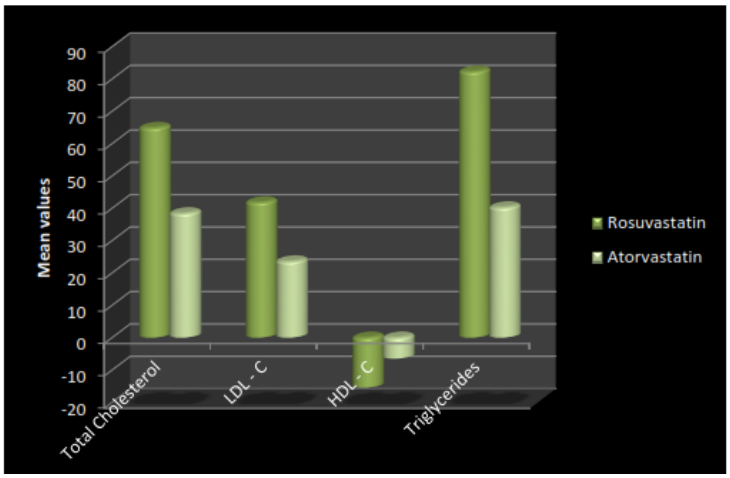

Figure -1: Bar graph showing comparison of lipid parameters between atorvastatin and rosuvastatin group

SAFETY PARAMETERS

There was no clinically significant changes Creatine kinase and Liver Function Test in both the treatment groups, both Rosuvastatin and Atorvastatin were found to be safer drugs. (Table-6, 7)

Table 6: Comparison of raise in creatine kinase between Group 1 and Group 2

Clinical Variable	GROUP-1 (ROSUVASTATIN) Difference between before & after N=30	GROUP-2 (ATORVASTATIN) Difference between before & after N=30
Creatine Kinase (in mg/dl)	0	0

Table 7: Comparison of liver function tests between group 1 and group 2

Clinical Variables	GROUP-1 (ROSUVASTATIN) Difference between Before & After N=30		GROUP-2 (ATORVASTATIN) Difference between Before & After N=30		Unpaired t test df=28, p values
	Mean	Std Deviation	Mean	Std Deviation	
Total Bilirubin	0.36	0.22	0.01	0.21	0.81, NS

Direct Bilirubin	0.06	0.14	0.00	0.09	2.02, P<0.04
Indirect Bilirubin	0.19	0.17	0.006	0.16	0.29, NS
Total Protein	0.05	0.75	0.07	0.63	0.19, NS
A. Albumin	0.12	0.47	0.14	0.47	0.16, NS
A. Globulin	0.06	0.43	0.7	0.33	0.03, NS
SGOT	0.47	4.91	0.9	5.94	0.31, NS
SGPT	0.56	6.74	1.66	5.87	0.67, NS
Alkaline Phosphatase	0.86	19.95	5.06	15.17	1.29, NS

Both the treatment group were well tolerated during the course of intervention.

DISCUSSION

The present study was a prospective open label observational study comparing efficacy and safety of rosuvastatin with atorvastatin in patients with metabolic syndrome.

The reduction of Total Cholesterol (TC) levels between the rosuvastatin and atorvastatin group, from baseline was 64.87 mg/dl and 38.43mg/dl respectively, which was statistically significant (P <0.001). On comparing the 2 groups, the rosuvastatin group had a greater reduction than the atorvastatin group, which was statistically significant (P < 0.01).

The reduction of Triglycerides (TG) levels between the rosuvastatin and atorvastatin group, from baseline was 82.3 mg/dl and 40.26 mg/dl respectively (p <0.001). On comparing, the reduction between the 2 groups, reduction in triglycerides was greater with rosuvastatin and was statistically significant (P < 0.005).

The reduction of Low Density Lipoprotein (LDL) levels between the rosuvastatin and atorvastatin from baseline was 41.83 mg/dl and 23.56 mg/dl respectively, which was statistically significant (P <0.001). On comparing the 2 groups, the rosuvastatin group had a greater reduction than the atorvastatin group, which was statistically significant (P < 0.02).

The mean change of High Density Lipoprotein (HDL) levels between the rosuvastatin and atorvastatin group, from baseline was 15.4 mg/dl and 6.47 mg/dl respectively, which was statistically significant (P <0.001). On comparing the 2 groups, the rosuvastatin group had a greater percent of change than the atorvastatin group, which was statistically significant (P < 0.001).

From the Tables – 6, 7 it is seen that the changes in liver function tests and creatine kinase levels were not significant in both rosuvastatin and atorvastatin group. Even after inter group comparison both drugs were found to be equally safer.

Various studies have evaluated the efficacy of rosuvastatin and atorvastatin. The results obtained from the present study are consistent with the following studies.

In a PULSAR study, a prospective study by Michael B Clearfield, John Amerena et al to evaluate the efficacy and safety of rosuvastatin 10mg and atorvastatin 20mg in high risk patients with hypercholesterolemia, Rosuvastatin 10 mg increased HDL-C levels and decreased LDL-C levels to a significantly greater extent than atorvastatin 20mg, while similar reductions in TC, TG, and non HDL-C levels were observed with both drugs. Both treatments were well tolerated, with a similar incidence of adverse events and no cases of rhabdomyolysis, liver, or renal insufficiency were recorded. [18]

In the DISCOVERY study, twelve week, randomized, multicentre study in patients with CHD and hypercholesterolemia, rosuvastatin 10 mg was associated with significantly greater reductions in LDL-C, TC levels and with a significantly greater increase in HDL-C levels compared to atorvastatin 10 mg and both agents were well tolerated. [19]

In URANUS study, by Christian Berne, Annica Siewert-Delle et al comparing atorvastatin and rosuvastatin in patients with type 2 diabetes, rosuvastatin (10mg) was significantly more effective than atorvastatin (10mg) at reducing LDL-C. [20]

In a study comparing efficacy and safety of atorvastatin, rosuvastatin and simvastatin in patients with type 2 Diabetes Mellitus and dyslipidemia it was shown that 10mg of rosuvastatin was more efficacious than 10 mg of atorvastatin and simvastatin in increasing HDL cholesterol. [21]

In a study by Suyog Sindhu, Hemanth Kumar Singh et al it was concluded that rosuvastatin should be preferred over atorvastatin in obese type2 Diabetes Mellitus patients in whom LDL-C and TC was higher than reference values. [22]

Gregory G. Schwartz, Michael A. Bolognese et al in their randomized controlled trial proved that rosuvastatin was more efficacious than atorvastatin in modifying lipids in patients with hypercholesterolemia and a high coronary heart disease risk. [23]

In STELLAR trial by Peter H. Jones, Michael H. Davidson et al, rosuvastatin is more efficacious in reducing plasma low-density lipoprotein (LDL) cholesterol and achieving LDL cholesterol goals than atorvastatin, simvastatin, or pravastatin.[24]

It is stated in Bayesian meta-analysis that rosuvastatin reduced LDL-C level by 10 to 17% points more than atorvastatin when both were given at the same dose. Approximately one quarter of the dose of rosuvastatin reduced LDL-C level as atorvastatin at dosages as high as 80 mg but this finding does not imply a 4-fold difference in efficacy. [25]

Bullano MF , Wertz DA et al in their retrospective longitudinal cohort study concluded that rosuvastatin was more effective than other statins in reducing LDL, triglyceride and total cholesterol levels. Significantly more patients taking rosuvastatin than patients taking other statins attained their LDL goals. [26]

In usual clinical practice, rosuvastatin is more effective and cost-effective in lowering LDL-C and in attainment of ATP III LDL-C goals compared with atorvastatin or simvastatin among high-risk patients. [27]

Schwartz GG, Bolognese MA et al have demonstrated in their study that rosuvastatin was more efficacious than atorvastatin in modifying lipids in patients with hypercholesterolemia and a high coronary heart disease risk. [28]

Among elderly patients, rosuvastatin was more effective treatment for reducing LDL-C levels and attaining NCEP ATP III LDL-C goals than the other statins in routine clinical practice. [29]

In DISCOVERY PENTA study, by Fonseca FA , Ruiz A et al rosuvastatin treatment was associated with significant reductions in LDL-C and total cholesterol (TC) and, in statin-naïve patients, a significant increase in high-density lipoprotein cholesterol (HDL-C) compared with atorvastatin treatment. Both treatments were well tolerated with a similar incidence of adverse events. [30]

In a twelve-week, multicenter, randomized, open-label DISCOVERY study comparing rosuvastatin 10 mg/d and atorvastatin 10 mg/d in high-risk adults for CHD and with primary hypercholesterolemia by Strandberg TE , Feely J et al, rosuvastatin 10mg/dl was associated with significantly greater reductions in LDL-C and TC levels and significantly greater increase in HDL-C compared with atorvastatin 10 mg/dl. Furthermore both agents were well tolerated. [31]

Along with lipid lowering effect of statins they also have pleiotropic effects. Few studies where pleiotropic effects are proved are as follows.

Statins are developed as lipid lowering drugs, but have also shown to decrease morbidity and mortality from coronary artery disease. Stimulation of neovascularization is vital to rescue tissue from critical ischemia and it is demonstrated in a study conducted by Stefanie Dimmeler, Alexandra Aicher et al that statins increase number of endothelial progenitor cells both in vitro and in mice. [11,32,33]

The activity of HMG-CoAreductase limits the rate of synthesis of not only cholesterol but also of a range of other molecules involved in functions such as cellular respiration and cell-cell recognition. Therefore statins, as inhibitors of this enzyme, might modify constituents of the vascular milieu other than LDL cholesterol. [12]

Marika Massaro, Antonella Zampolli et al, show that statins reduce COX-2(Cyclo-oxygenase) and MMP-9(Metalloproteinase) expression and activity in the human vascular endothelium thus contributing to plaque stability a cholesterol-lowering-unrelated protective effect. [34]

CONCLUSION

Metabolic syndrome is a growing epidemic in India consisting of metabolic abnormalities like insulin resistance, obesity, hypertension and dyslipidemia. The subjects of metabolic syndrome are at greater risk of coronary heart disease which increases rate of mortality and morbidity.

Statins are the drugs which are shown to reduce lipid levels and with their pleiotropic effects are also beneficial in prevention and treatment of coronary heart disease in metabolic syndrome patients.

So in this study, rosuvastatin has shown significantly greater efficacy in comparison to atorvastatin in lowering lipid levels and both drugs were found to be equally safe in subjects with metabolic syndrome.

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