LIPID-LOWERING EFFICACY OF 20 MG SIMVASTATIN VERSUS 5 MG ROSUVASTATIN IN PATIENTS OF TYPE 2 DIABETES

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ABSTRACT

Objective: To compare the efficacy of Rosuvastatin 5mg and Simvastatin 20mg in reducing low-density lipoprotein cholesterol in newly diagnosed patients with type 2 diabetes.
Study Design: Quasi-experimental study.
Place and Duration of Study: Department of General Medicine, Pak Emirates Military Hospital (PEMH), Rawalpindi, from Jul 2017 to Jan 2018.
Methodology: Patients of type 2 diabetes with hypercholesterolemia (mean LDL-C levels >100 mg/dl) were included in the study. In a sample of 100 patients, half of the patients were in the Rosuvastatin 5mg group (group A) while half patients were in the Simvastatin 20mg group (group B). Non-probability consecutive sampling was done. We followed up the patients for 6 weeks. All the laboratory investigations were performed from the laboratory of the same hospital. Investigator himself recorded all the information including name, age, gender, weight, LDL-C levels, Renal function test reports and CK-MB levels in a self-designed, self-administered proforma. Data were analyzed with statistical analysis program SPSS V 23.
Results: Age range in this study was from 35 to 60 years with a mean age of 46.980 ± 6.31 years in group A vs 48.520 ± 5.61 years in group B. Mean LDL-C Levels were 149.460 ± 25.76 mg/dl in group A vs 146.960 ± 22.92 mg/dl in group B. Mean weight was 82.880 ± 9.17 kg in group A vs 88.660 ± 10.33kg in group B. Male gender was dominant in both group (70% and 72%). In group A, efficacy was seen in 40 (80%) patients as compared to 24 (48%) patients in group B (p<0.001).
Conclusion: Rosuvastatin 5mg tablet was more effective than Simvastatin 20mg in reducing low-density lipoprotein cholesterol in newly diagnosed type 2 diabetes patients.

Keywords: HMG-CoA reductase inhibitor, Lipid-lowering efficacy, Low-density lipoprotein cholesterol, Rosuvastatin, Simvastatin, Type 2 diabetes mellitus (T2DM).

INTRODUCTION

Diabetes mellitus is recognized as one of the leading diseases with high morbidity and mortality across the globe and constitutes a major percentage of the burden imposed by non-communicable diseases. In the Middle Eastern and North African region (MENA), 39 million people are living with diabetes mellitus and this figure is expected to rise to 67 million by the end of the year 2045. According to the International Diabetes Federation (IDF) survey, Pakistan has 7,474,000 adults with diabetes making it 6.9% of the total adult population[1]. Type 2 diabetes is the commonest form of diabetes comprising 80-90% of the total diabetic patients[2].

Dyslipidemia is one of the commonest associations with diabetes[3]. Atherosclerotic changes and dyslipidemias are directly related to one another[4]. Patients of type 2 diabetes with hypercholesterolemia i.e. LDL-C levels >70 mg/dl and age group of 40-75 years are at increased risk of atherosclerotic cardiovascular disease (ASCVD) events and death. Importantly there is a piece of stronger evidence that the use of moderate to high-intensity statin therapy in this certain population for primary prevention is supported and is found to reduce the risk of chronic heart diseases[5]. Those patients of diabetes who experienced even a single episode of clinical

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ASCVD suffer greater morbidity and have the worse outcome thus imposing a huge socio-economic burden on the healthcare system[6].

Adoption of a healthy lifestyle is recommended before and along with the use of cholesterol-lowering medicines as background therapy proved to reduce ASCVD risk several folds. Essential components of primary and secondary prevention in patients of diabetes with hyper-cholesterolemia for ASCVD include lifestyle modification and statin therapy. These patients must obey strict adherence to anti-hyperlipidemic therapy[6]. Multiple studies on the lipid-lowering effect of statins revealed a significant result in Asian populations as compared to caucasians owing to different genetic and epigenetic mechanisms involved[7,8].

Certain studies also suggested that low dose statins are quite effective for primary prevention in Asian populations with low to moderate ASCVD risk. Rosuvastatin; an HMG-CoA reductase inhibitor showed a high post-administration plasma concentration in Asians as compared to whites[9].

Simvastatin, however, when administered as monotherapy, has shown lesser effectiveness in terms of lipid-lowering in one randomized control trial[10].

We designed this study to compare the mean LDL-C reduction efficacy of moderate-intensity Rosuvastatin 5mg with Simvastatin 20 mg administered per oral at night in our native population. Limited research work has been conducted in our local population comparing these two monotherapies in a single clinical study in newly diagnosed patients of type 2 diabetes with hyper-cholesterolemia (LDL-C levels >100 mg/dl). The population at risk which participated in this study has never been on statin therapy before enrollment in this clinical study.

METHODOLOGY

It was a quasi-experimental study carried out from July 2017 to January 2018 at the department of General Medicine, Pak Emirates Military Hospital (PEMH); a tertiary care hospital in Rawalpindi. Newly diagnosed patients with type 2 diabetes and hypercholesterolemia (mean LDL-C levels >100 mg/dl) were included in the study. A sample size of 100 patients was calculated by a WHO sample size calculator with a reference prevalence of 6.9%[1]. Half patients were in the rosuvastatin 5mg group (group A) while half of patients were in the simvastatin 20mg group (group-B). Non-probability consecutive sampling was done. We ensured the confidentiality of each participant's data and used single-blind balloting to randomly assign subjects into one of the two groups of 50 patients each. Efficacy was defined as <100 mg/dl fasting LDL-C level after consecutive 6 weeks of statin therapy. A fasting blood glucose level of >126 mg/dl (>7.0 mmol/l) at two different occasions & or HbA1C >6.5% on a single lab test defined a patient of diabetes. Inclusion criteria were newly diagnosed patients with type 2 diabetes as per operational definition, of age group 35 to 60 years & LDL-C level ≥100 mg/dl on a single lab test at the time of enrollment. Exclusion criteria were a history of anti-hyperlipidemic drug intake in the past 1 year and hypercholesterolemia based on family history. Patients who fulfilled the inclusion criteria were enrolled in the study from the Department of General Medicine, Pak Emirates Military Hospital, Rawalpindi after informed written consent, detailed interview and counseling on a volunteer basis. We obtained approval from the institutional ethics review committee (PEMH 23/03) and all ethical concerns were discussed and addressed. The day of patient enrolment was labeled as visit '0' and we collected baseline demographic information (age, gender, weight), fasting LDL-C levels, renal function tests, and CK-MB levels. We gave Rosuvastatin (5mg/day) to the patients in 'group A' vs patients in 'group B' received Simvastatin (20 mg/day) for 6 complete weeks. We followed up the patients at 3 weeks labeling it as Visit '1' and at 6 weeks labeled as Visit '2'. All the lab tests were repeated at each visit. Renal function tests (RFTs) and CK-MB were done to look for possible adverse effects

of drug therapy. No patient reported poor compliance and none was lost to follow up. All the laboratory investigations were performed from the laboratory of the same hospital under the supervision of a single expert pathologist with an experience of 10 years in the field. Investigator himself recorded all the information including name, age, gender, weight, LDL-C levels, RFT reports and CK-MB levels in a self-designed, self-administered proforma. Data were analyzed with statistical analysis software (SPSS-23).

RESULTS

The age range in this study was from 35 to 60 years with a mean age in group A and group B was 48.520 ± 5.61 vs 46.980 ± 6.31 years. Mean baseline LDL-C Levels in group A and group B were 149.460 ± 25.76 mg/dl vs 146.960 ± 22.92 mg/dl. Mean weight in group A and group B was 82.880 ± 9.170 kg vs 88.660 ± 10.331 Kg.

Table-I: Stratification of Efficacy with respect to LDL-C levels in group A and group B.

For 100-160 mg/dl			
	Efficacy		*p*-value
Groups	Yes, n(%)	No, n(%)	
A (Rosuvastatin 5mg)	32 (100)	-	<0.001
B (Simvastatin 5mg)	24 (66.7)	12 (33.3)	
For >160 mg/dl			
A (Rosuvastatin 5mg)	8 (44.4)	10 (55.6)	0.004
B (Simvastatin 5mg)	-	14 (100)	

Table-II: Stratification of efficacy with respect to weight in group A and group B.

For ≤70 kg			
	Efficacy		*p*-value
Groups	Yes, n(%)	No, n(%)	
A (Rosuvastatin 5mg)	8 (88.9)	1 (11.1)	0.206
B (Simvastatin 5mg)	3 (60)	2 (40)	
For >70 kg			
A (Rosuvastatin 5mg)	32 (78)	9 (22)	0.002
B (Simvastatin 5mg)	21 (46.7)	24 (53.3)	

In group A there were 35 (70%) males and 15 (30%) females while in group B there were 36 (72%) males and 14 (28%) females. In group A, efficacy was seen in 40 (80%) patients as compared to 24 (48%) patients in group B, (p=0.000). Stratification of efficacy for age in group A and group B showed efficacy in 25 (83.3%) of group A and 11 (55%) patients of group B (p-value 0.028) in the age group 35-48 years of age. In the age group, 49-60 years efficacy was shown in 15 (75%) of group A and 13 (43.3%) patients of group B (p-value 0.027). Stratification of efficacy for gender in group A and group B showed efficacy for male gender in 31 (88.6%) patients of group A and 18 (50%) patients of group B (p-value <0.001). For female gender efficacy was shown for 9 (60%) patients in group A and 6 (42.9%) patients in group B (p-value 0.355). Only one patient of group A reported with mild derangement of RFTs at visit '2'.

Stratification of efficacy for LDL-C levels and weight are shown in table-I & II.

DISCUSSION

For atherosclerotic cardiovascular diseases (ASCVD) hyperlipidemia is a modifiable risk factor[11]. AHA/ACC guidelines 2013 recommend the use of statin therapy for patients of diabetes with hypocholesteremia as they are at risk population for ASCVD. Pakistan is a country with every fourth adult with diabetes mellitus and the recent AHA/ACC 2013 guidelines impart a huge burden upon the healthcare system and economy of the country by increasing the potential receivers of anti-hyperlipidemic therapy. A variety of statins are available in the market in different dosages and costs. The majority of people in Pakistan don't even know about their diabetes status owing to the limited accessibility of screening & diagnostic tests for diabetes mellitus by a majority of the population. The country still lacks a national diabetes registry and evidence-based national diabetes guidelines[12]. Statin therapy ensues multiple adverse effects owing to the type and dosage of particular statin warranting its careful selection according to the individual to

provide maximum targeted care in primary and secondary prevention of cardiovascular diseases[6]. The statins used frequently in our setup are Rosuvastatin and Simvastatin in different dosage and it is wise to ascertain the efficacy of different statins for better patient care and cost-effectiveness in our local population setup. Lee *et al*, found that Asians already showed that statins are required in a lesser dosage to build effective plasma concentration in this particular population[7,8]. Brunetti *et al*, shared that Daunia registry enrolled 661 patients of congestive cardiac failure (CCF) and compared the outcomes in terms of mortality following anti-hyperlipidemic therapy of each of the three statins i.e. Rosuvastatin, Simvastatin, and Atorvastatin. Atorvastatin and Rosuvastatin were found superior in reducing mortality to Simvastatin (4%, 4%, and 15% mortality rate respectively)[13]. A recent study revealed that patients with normal LDL-C levels may also develop chronic heart disease due to elevated small density LDL-C (sdLDL-C) levels[18].

In our study, the mean age of the participants in group A receiving rosuvastatin was 46.980 ± 6.31 years vs 48.520 ± 5.61 years in group B receiving Simvastatin 20 mg comparable to mean age of 55.46 ± 9.76 years 14 vs 55.46 ± 9.76 years[15] in groups receiving rosuvastatin 5 mg of respective studies. Brown *et al*, found out that participants in the group receiving Simvastatin 20mg have a mean age of 62 ± 14 years and 58 ± 11 years in rosuvastatin 5 mg group. There were 35 (70%) males in group A of this study while 36 (72%) males in group B of this study[16]. A study conducted by Ullah *et al*, showed that 35 (42.68%) male patients received rosuvastatin 5mg[14] and Kong *et al*, revealed 60 (50%) male patients were in the group receiving rosuvastatin 5mg[15]. Jeong *et al*, reported that 48 (46.2%) and 150 (46%) participants of male gender in the group receiving Rosuvastatin 5mg & Simvastatin 20 mg respectively[17].

Mean weight was 82.880 ± 9.17 kg in group A vs 88.660 ± 10.33kg in group B in this study. Kong *et al*, had a mean BMI of 24.8 ± 3.1 in rosuvastatin 5 mg arm of study[15].

Mean baseline fasting serum LDL-C levels were 149.460 ± 25.76 mg/dl in rosuvastatin 5 mg group of this study comparable to Ullah *et al*, and his associates which reported mean LDL-C levels of 134.12 ± 30.02 mg/dl and Brown *et al*, observed 187.3 ± 17.8mg/dl mean baseline LDL-C levels in a similar group of study. Both these studies were carried out in different ethnicities, thus a slight difference in baseline LDL-C levels observed[14,16].

In this study, treatment with moderate-intensity statins in patients with newly diagnosed Type 2 Diabetes Mellitus (T2DM) achieved the LDL-C target goal (<100 mg/dL) in 80% of the participants with rosuvastatin 5mg and 40% with simvastatin 20mg. Stratification of efficacy for LDL-C levels in group A and group B showed that rosuvastatin 5 mg showed 100% efficacy (n=32) in patients with baseline LDL-C level 100-160 mg/dl as compared to 24 (66.7%) by Simvastatin 20 mg, (p=0.000). Simvastatin 20 mg was less effective in patients with LDL-C levels. 170 mg/dl (0% efficacy) as compared to 8 (44%) efficacy by Rosuvastatin 5 mg, (p=0.004). The results of our study are comparable to Ullah *et al*. who observed mean reduction of significant 52.51 ± 19.49 mg/dl in the Rosuvastatin 5mg group at 6 weeks[14].

When efficacy with respect to weight in group A and group B is stratified, it showed that Rosuvastatin 5 mg showed 88.9% efficacy (n=8) in patients with weight ≤ 70 Kg as compared to 3 (60%) by Simvastatin 20 mg, (p=0.206). Simvastatin 20 mg was less effective for >70kg weight patients; 46.7% efficacy (n=21) as compared to 32 (78%) efficacy by Rosuvastatin 5 mg, (p=0.002).

Brown *et al*, communicated a 39.1% reduction in LDL-C levels with Rosuvastatin 5 mg and 34.6% with Simvastatin 20 mg at 12 weeks[16]. Kong *et al*, concluded that the efficacy of Rosuvastatin 5 mg in reducing serum LDL-C levels in patients of type 2 diabetes was 95%[15]. Jeong *et al*, observed mean LDL-C reduction of 41.5 ± 1.6 & 36.5 ± 1.0% reduction for Rosuvastatin 5 mg and Simvastatin 20 mg in the Korean population and concluded that Rosuvastatin is more cost-

effective in an observational registry data[17]. We measured the CK-MB levels and renal function tests before enrolment of the patients in this study and at visit 1 and visit 2 to observe for the possible adverse effects of these statins. Liver function tests were only recommended by AHA/ ACC 2013 in case the patients displayed any signs and symptoms of liver toxicity[6].

CONCLUSION

Rosuvastatin 5mg tablet was more effective than Simvastatin 20mg in reducing low-density lipoprotein cholesterol (LDL-C) in newly diagnosed patients of type 2 diabetes. We recommend further multicenter clinical studies for different commonly prescribed statins at a different dosage which will ultimately pave the road towards the development of national evidence-based guidelines and ASCVD risk scoring in our population.

Disclosure

This scientific paper was presented in "16th International Electrophysiology Conference at AFIC Rawalpindi" and won 2nd prize in a poster competition held at this conference held in February 2019.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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