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Comparison of Low Dose Versus High Dose Statin Therapy in Improving Dyslipidemia

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ABSTRACT

Dyslipidemia, a significant contributor to atherosclerosis and its associated conditions like coronary artery disease, cerebrovascular disease, and peripheral vascular disease, requires effective management through lifestyle changes and pharmacological treatment. Statins are commonly used to reduce low-density lipoprotein (LDL) cholesterol levels, thus lowering the risks of myocardial infarctions and strokes. However, higher doses of statins, while more effective in reducing cardiovascular events, are associated with an increased risk of adverse effects such as myopathy and elevated liver enzymes. This study aimed to compare the efficacy of low-dose (10 mg) versus high-dose (40 mg) atorvastatin therapy in improving lipid profiles in patients with acute coronary syndrome (ACS).

A randomized trial was conducted with 90 ACS patients recruited from the Bolan Medical Complex, Quetta. They were randomly assigned to either receive 10 mg or 40 mg atorvastatin daily for four months. Lipid profiles, including HDL-C, LDL-C, triglycerides, and total cholesterol, were measured before and after the intervention. Both dosage groups showed significant improvements in their lipid profiles after the treatment period. However, there was no statistically significant difference between the two groups in the overall improvement of dyslipidemia.

These findings suggest that both low and high doses of atorvastatin are effective in improving lipid profiles, but higher doses may not offer additional benefits in this patient population.

INTRODUCTION

Dyslipidemia is a major cause of atherosclerosis and atherosclerosis-associated conditions, such as coronary artery disease (CAD), ischemic cerebrovascular disease, and peripheral vascular disease. Treatment should focus on weight loss, physical activity and drugs. The goals of treatment are listed in decreasing order of atherogenicity due to low density lipoprotein (LDL), very-low-density lipoprotein (VLDL) and chylomicrons. A desirable total cholesterol level in low- HDL-C patients may be considerably lower than 200 mg/dl (felitti VJ, Goodman & Gilman; 2006) (Harvey RA, et al., 2012) Statin decrease LDL. And cholesterol synthesis. Furthermore, in high doses it reverses plaque growth and plaque stabilization. Study by Chang et al) reported the improvement in LDL-C in 55.8% vs 82.4%, total cholesterol 42% vs 71% in patient receiving 10mg vs 40

mg atorvastatin respectively. Another study reported High-dose statin therapy significantly reduced the sd-LDL. and MDA-LDL components of atherosclerotic lipoproteins without adverse events in comparison with low-dose statin therapy (Nishikido et al., 2016)) Study by Mansour et al (Mansour H; 2017) demonstrated no significant difference between high and low dose of atorvastatin. To manage dyslipidemia and that both reduce the risk of coronary It is worth mentioning that dyslipidemia presents with elevated or reduced level of lipids in the blood and is a substantial CVD risk factor; CVD remains the leading cause of death in the world according to the World Health Organization (World Health Organization, 2023). Stone et al. , (2013) acknowledges that dyslipidemia manifests by; reduced HDL-C and elevated triglycerides, total cholesterol and LDL–C. Oron et al (2016) stated that prevention of dyslipidemia is crucial to decrease atherosclerotic cardiovascular disease (ASCVD) which comprises of myocardial infarction and stroke. Statins, which is the abbreviation for HMG-CoA reductase inhibitors, is the most common drug used to treat dyslipidemia because of their bid impact on reducing LDL-C (Grundy et al. , 2018). They act in the inhibition of HMG-CoA reductase enzyme which it is an important catalyst through the cholesterol synthetic pathway resulting in decreased cholesterol synthesis in the liver (Goldstein & Brown, 2015).

Clinical practice treatment of dyslipidemia is never easy. Indians are becoming more and more likely to have dyslipidemia, even in younger age groups. In addition, the dyslipidemia pattern differs greatly from those of Western nations. (Enas EA & Salim Yusuf Mehta JL; 2018) When it comes to the treatment of high-risk ASCVD (atherosclerotic cardiovascular disease) patients, statins are crucial. (Newman C, Tsai J, Szarek M, et al; 2006) Study by Mansour et al (Mansour H; 2017) demonstrated no significant difference between high and low dose of atorvastatin.

It was further showed that the high dose statin therapy offers LDL-C level control that is superior to that achieved by low dose therapy. For instance, Chang et al. , (2013) affirmed that at a dose 40mg of atorvastatin had a reasonably progressive effect on lipid profiles and atorvastatin 10mg had more reduction in the total cholesterol and LDL-c. Using the findings of Chang et al. (2013), For example, Waters et al. (2012) have reported that patients receiving high doses of statins are at higher risk of new onset diabetes although development of myocardial infarction or stroke is reduced. High-degree patient selection and endeavoring are required because high statins dosage may incite more sullying outcomes in patients with other chronic diseases that place them at risk of such consequences.

RATIONALE OF THE STUDY

The rationale for this study is to close the information gap about the effectiveness of low-dose versus high-dose statin medication in treating dyslipidemia in patients from Pakistan. This entails tracking for any adverse effects and evaluating changes in lipid markers, such as triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). This project is to produce evidence-based recommendations that can guide clinical practice and enhance cardiovascular health outcomes in our community by identifying the most efficient dosage approach. Optimizing statin therapy is essential for lowering the overall healthcare burden and improving the quality of life for patients with dyslipidemia, especially considering the high prevalence of cardiovascular diseases and the financial constraints in Pakistan. Additionally, the research findings may be used to inform healthcare policy and resource allocation, ensuring that patients receive the most appropriate and economical treatment.

LITERATURE REVIEW

There is a possibility of increasing the side effect of myopathy, high serum creatine kinase, and newly developed diabetes mellitus with high-dose statin medication (Preiss et al., 2011). Low intensity statin therapy however associated with low side effect profile; however probably not as effective helping high risk patient achieve their cholesterol goals (Robinson et al., 2016). There is always the question of whether increasing the effectiveness of dyslipidemia treatment can also enhance risk mitigation – or if it is a trade-off. The latest cholesterol management guidelines set by the ACC/AHA call for high dose statin use in patients with high risk of ASCVD whereas moderate-intensity statin is advised in those with lower risk or intolerance to high dose (Grundy et al. , 2019). Meta-analysis shows that low/moderate-intensity statin plus ezetimibe improved lipid levels more than high-intensity statin monotherapy, and that statin monotherapy increased ALT and CK more than statin/ezetimibe combination therapy. (Ah, Y. M., Jeong, M., & Choi, H. D. (2022). The second generation statins, atorvastatin and simvastatin, have significantly improved efficacy in reducing LDL-C levels compared to the earlier statins; finally, there is a single commercially available drug in the third, high-potency generation of statins, rosuvastatin. Three unique chemical characteristics of rosuvastatin provide enhanced potency against HMG-CoA reductase. (Zhang, X., Xing, L., Jia, X., Pang, X., Xiang,(2020). In conclusion, combination therapy with ezetimibe 10 mg and rosuvastatin 5 mg compared with rosuvastatin 20 mg did not meet the criterion for non-inferiority for primary outcome, and the present study was not

conclusive on whether the former was non-inferior to the latter. (Oh, M., Kim, H., Shin, E. W., Sung, C., Kim, D. H., Moon, D. H., Kim, N., Eo, J. S., Kim, J. W., & Lee, C. W. (2020).

The Roseze trial is expected to demonstrate whether there is a significant difference in the effectiveness of the lipid-lowering therapy in reducing the concentration of cholesterol when the medications are taken in the morning compared with the evening time of day hypercholesterolemia is one of the main risk factors for cardiovascular disease. The first line treatment for hypercholesterolemia is statin therapy. When the expected low-density lipoprotein cholesterol (LDL-C) concentration is not achieved, the pharmacotherapy may be extended by combining the statin with the cholesterol absorption inhibitor ezetimibe.(Obońska, K., Kasprzak, M., Sikora, J., Obońska, E., Racki, K., Goździkiewicz, N., Krintus, M., & Kubica, J. (2017). Fixed-dose combinations of ezetimibe/rosuvastatin significantly improved lipid profiles in patients with hypercholesterolemia compared with rosuvastatin immunotherapy. Hong, S. J., Jeong,. W., … Kim, H. S. (2018). The mechanism of action of the statins – HMG-CoA reductase inhibitors is achieved by binding to the active site of the enzyme HMG-CoA reductase which is crucial in a pathway leads to the synthesis of cholesterol. As a consequence, hepatocytes' LDL receptors are upregulated This also reduces liver cholesterol synthesis and enhances the clearance of LDL-C from the circulation (Endo, 1992). The potency of statin therapy is described us low, moderate, and high intensity that Table 1 indicates the effects of these categories on lipid concentrations and CVD risk reduction (Stone et al., 2014). There is evidence of side effects with the use of high dose statin therapy hence the need to have proper patient management and follow up. Close monitoring of creatine kinase, and liver enzymes should be done periodically in the patients under this kind of treatment. Known risk factors are; female gender, history of renal disease, older age and presence of other drugs that would interact with statins. Statin myopathy and rhabdomyolysis rates are low; rates rise with high-dose statin (Thompson et al., 2016)

OBJECTIVE

- To compare the low dose versus high dose statin therapy in improving dyslipidemia in patients with acute coronary syndrome.

OPERATIONAL DEFINITION

Acute Coronary Syndrome: Presence of any one of the following: Unstable Angina: It is defined as typical chest pain (substernal crushing chest pain radiating towards left shoulder or left arm) occurring at rest or on exertion not relieved by rest or sublingual nitrates

Non-STEMI: Non-ST-elevation myocardial infarction (NSTEMI) is an acute ischemic event causing myocyte necrosis, will be diagnosed in patient with the all of the following criteria; + Typical chest pain >20 minutes (retrosternal pain with radiation to left arm or shoulder, aggravates on exertion or emotional stress)

- Typical chest pain >20 minutes (retrosternal pain with radiation to left arm or shoulder, aggravates on exertion or emotional stress)
- ECG at presentation showing any of ST depression (>= 2mm), transient ST elevation (2 2mm), and/or prominent T-wave inversions.
- The typical rise of cardiac troponin one value above the upper limit of normal range (>0.05 ngdL /for male and > 0.03ng / d * L for female).

ST Elevated Myocardial Infarction: It will be labelled if following features will be present:

- Typical chest pain >20mins (retrosternal pain with radiation to left arm or shoulder, aggravates on exertion or emotional stress).
- ST segment elevation in 2 or more contiguous leads or new Left bundle branch block. ST segment elevation will be considered if J-point elevation greater than 2mm in lead V2 and V3 and >= 1 Imm in all other leads.

Dyslipidemia: It will be labelled as positive if any of the following condition will be present:

- Total cholesterol > 200mg / dl .
- Triglycerides > 150mg / dl
- LDL cholesterol > 100mg/dl.
- HDL cholesterol < 40mg / dl for men and < 50mg / dl for women.

Improvement in Dyslipidemia: Improvement will be label if lipid profile of patient becomes normal i.e

- Total cholesterol <= 200mg dI .
- Triglycerides <= 150mg / dl .
- LDL cholesterol ≤ 100mg/dl.
- HDL cholesterol ≥40mg/dl for men and ≥50 mg/dl for women.

MATERIAL & METHODS

Study Design: This study was conducted as a randomized controlled trial (RCT) to compare the efficacy of low-dose (10 mg) versus high-dose (40 mg) atorvastatin in improving dyslipidemia in patients with acute coronary syndrome (ACS).

Study Setting: The trial was carried out in the Department of Cardiology at Bolan Medical Complex Hospital, Quetta.

Sample Size: The sample size was calculated using the WHO sample size calculator based on the following assumptions: the rate of improvement in dyslipidemia was 42% in patients receiving 10 mg atorvastatin and 71% in those receiving 40 mg atorvastatin. With a power of 80%, the sample size determined was 90 patients, divided equally into two groups of 45 each.

Sampling Technique: The study utilized consecutive sampling to recruit participants.

Inclusion Criteria: The inclusion criteria included patients aged 18-70 years, both genders, those diagnosed with ACS, and those with dyslipidemia.

Exclusion Criteria: Patients with a prior history of dyslipidemia already on lipid-lowering therapy were excluded from the study.

DATA COLLECTION

Copies will be taken from College of Physicians and Surgeons Pakistan (CPSP) and concerned authorities of the institute after its initiation. All patients with acute coronary syndrome satisfying the inclusion criteria will be recruited from cardiology OPD of Bolan medical complex Quetta. However, prior to enrolment written informed consent will be obtained from each patient. During the enrollment, clinical and demographic data which include; age, sex, location of residence, family monthly income, height (measured using a wall mounted scale with shoes and cap off), weight (measured using a digital weighting machine while dressed in lightweight clothing), and BMI (weight ,height, volume diabetes (past medical history of diabetes and currently under treatment with anti-diabetic drugs for the last 6 months). The following underlying diseases will be taken and noted in a predesigned proforma: hypertension (patient has known history of hypertension and is on anti-hypertensive from last 6 months) and smoking (patient is smoking 5 or more cigarettes per day…last 2 years). Blood sample of 5 cc each of all patients will be collected after 12 hours of fasting. Blood sample will be collected by phlebotomist using aseptic method from participants for analysis. All patient will be randomly divided into 2 groups by using opaque sealed envelope method. Patient in group A will receive 10mg atorvastatin and group B will receive 40mg atorvastatin HS for 4 months. All patients will be called for follow-up after 4 months of starting treatment for the assessment of lipid profile. After 4-month treatment 5 cc blood sample will be taken after 12 hours fasting for the assessment of lipid profile. Improvement in dyslipidemia will be assess as per criteria mention in operational definition.

DATA ANALYSIS

Data will be analyzed by using SPSS version 24. Quantitative variables such as age, height, weight, BMI, family monthly income and lipid profile (total cholesterol, triglyceride, LDL and HDL) will be reported as mean and SD. Qualitative variables such as gender, residence, diabetes, hypertension, smoking and improvement in dyslipidemia will be reported as frequency and percentage. Improvement in dyslipidemia will be compared between both groups by using chi-square test. Confounding variables such as age, gender, residence, family monthly income, BMI, diabetes, hypertension and smoking will be controlled through stratification. Post stratification chi-square test will be applied, taking p-value ≤ 0.05 as significant.

RESULTS

In this study, 90 patients are included to collect the information low-dose versus high-dose statin medication in treating dyslipidemia. Data regarding different variables such as; age, height, weight, BMI, family monthly income and lipid profile (total cholesterol, triglyceride, LDL and HDL) gender, residence, diabetes, hypertension, smoking and improvement in dyslipidemia are collected through the Performa at Bolan Medical Complex Hospital, Quetta and the results were analyzed as: The mean ± SD of age was 44.08 ± 13.190 with C.I (41.33….46.82) years. The mean ± SD of height was 4.041 ± .3026 cm with C. I (3.978 4…104) cm . The mean ± SD of weight was 90.97 ± 24.052 with C. I (85.96….95.98) kg . The mean ± SD of BMI was 25.41 ± 5.106 with C.I (24.34…. 26.47). The mean ± SD of Income was 51098.90 ± 21982.344 with C.I (46520.86… 55676.95). In the Frequency distribution table of gender 45 (50%) were male while 45 (50%) were female patients. In the Frequency distribution table of Residence 50 (55%) were urban while 40 (45%) were rural patients. In the Frequency distribution table of comorbid 55 (60.5%) said yes while 35 (39.5%) said no. In the Frequency distribution table of smoking 52 (46.9%) said yes while 38 (53.1%) patients said no. In the Frequency distribution table of improvement in dyslipidemia 50 (55%) said Hematemesis while 40 (45%) said melena. Figure 1, 2, 3, 4, 5, 6 shows the graphical representation of gender, residential status, comorbid, smoking, and improvement in dyslipidemia respectively. Stratification of group, age, gender, residence (urban or rural), income, BMI, Comorbid, smoking, lipid profile at baseline, ad lipid profile after 4 months was done with respect to improvement in dyslipidemia to assess statistical differences

Table 1
Frequency distribution of smoking

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	53	8.1	58.2	58.2
	No	38	5.8	41.8	100.0
	Total	91	13.9	100.0	
Missing	System	562	86.1		
Total		653	100.0		

Table 1
Frequency distribution of improvement in dyslipidemia

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	50	7.7	54.9	54.9
	No	40	6.3	45.1	100.0
	Total	90	13.9	100.0	
Missing	System	562	86.1		
Total		653	653	100.0	

Figure 1
Frequency of residence

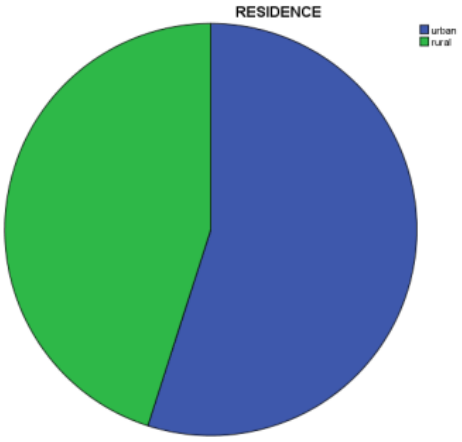

Figure 2
Frequency of Gender

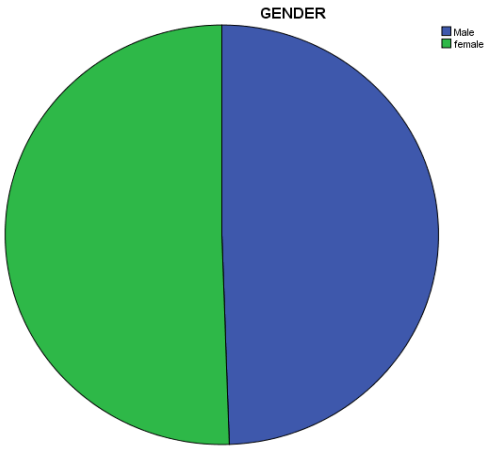

Figure 3
Frequency of comorbid

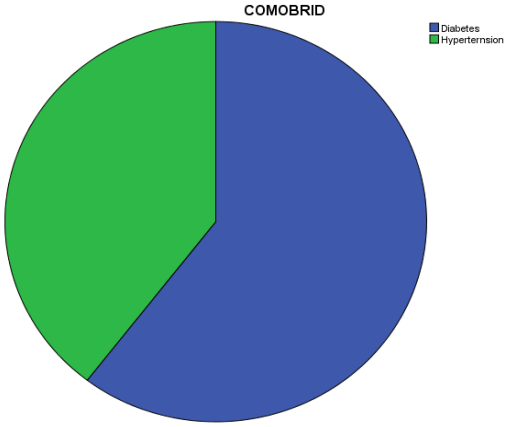

Figure 4
Frequency of smoking

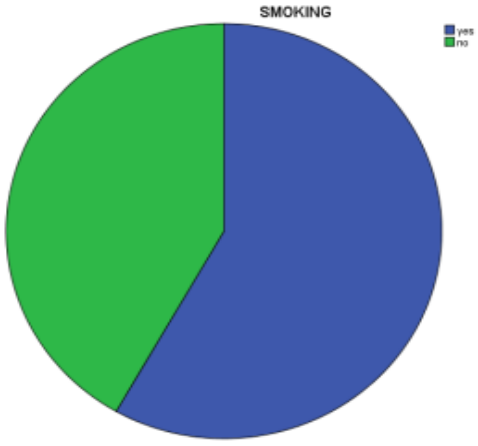

Figure 5
Frequency of improvement in dyslipidemia

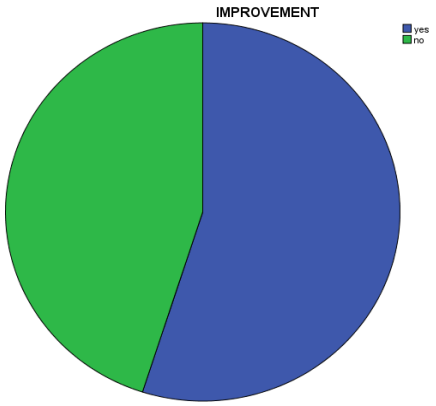

Table 3
Stratification of smoking with improvement in dyslipidemia

Smoking	Improvement in Dyslipidemia		P-value
	Yes	No	
Yes	35	18	0.18
No	15	22	

DISCUSSION

The purpose of the "Comparison of Low Dose Versus High Dose Statin Therapy in Improving Dyslipidemia" research was to evaluate how well individuals with acute coronary syndrome responded to 10 mg versus 40 mg of atorvastatin in terms of improved lipid profiles. Ninety patients in all were involved in the trial, and the results of the statin medication were examined in addition to their clinical and demographic features. The results of this study indicate that low dose as well as high dose atorvastatin might manage dyslipidemia in patients with ACS. Moreover, there is no significant distinction of the use of two dosage regimes: These results suggest that the management of dyslipidemia may be more effectively in the first instance giving atorvastatin and titrating it up depending on the side effects experienced by a patient. More subjects should be enrolled and longer follow-up duration should be employed in the subsequent research to offer indications on how to manage the dosing of statins in practice.

CONCLUSION

To assess the efficacy of 10mg of atorvastatin and 40mg of atorvastatin in managing lipid profiles in patients diagnosed with acute coronary syndrome (ACS), the study undertaken was “Low Dose Statin Versus High Dose Statin in Treatment of Dyslipidemia”. Therefore, ninety participants of both genders and of different ages and SES levels, to correspond to the disease comorbidities, were included in the randomized controlled trial. Thus, the research revealed that the most vital lipid fractions, including total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) had been enhanced through the effective research time of four months by both low-dose (10 mg) and high-dose (40 mg) atorvastatin. This is yet more evidence against the theory that the efficacy of atorvastatin depends on the patient’s number of characteristics that may require dosage adjustments. To this end, these implications hold significant significance to clinical practice. Further, the study failed to factor the degrees of compliance of patients with the lifestyle or pharmaceuticals prescribed them which might have accrued to the study in altering lipid profile. The studies also reveal that even at the low dosage of atorvastatin and high dosage of atorvastatin that men and women with ACS present signs of improvement in dyslipidemia without significant variation in response to dosage. These results suggest that despite patients on statin medication requiring to take their dosage in a lower dose starting point and titrating it in depending on their tolerance and response there is justification for this kind of approach to managing statin medication. We need to undertake larger sample size studies with longer follow up to confirm these findings and fine tune the ideal dosing schedules of statin therapy in clinical practice.

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