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Comparison between 20 mg versus 40 mg dose of atorvastatin among dyslipidemic patients associated with diabetes or coronary artery disease: a randomized clinical trial

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Abstract
Treatment of dyslipidemia among patients with diabetes or vascular disease improves patients' outcome. Statins are the most popular drugs used, but there is controversy on the optimum dose. In this study we aim to compare atorvastatin 20 mg versus atorvastatin 40 mg on lipid profile. Fifty five newly diagnosed patients suffering from dyslipidemia associated with diabetes or coronary artery disease aged(20–75) years with fasting total cholesterol concentrations (200 mg/L) or more and Triglyceride level 250 mg/L were randomly assigned to atorvastatin 20 mg or atorvastatin 40 mg. The lipid profile was taken at the start of study (baseline data) and after 6 months (final data). We planned follow-up for an average of 6 months. Data were analyzed using SPSS version 20. For statistical analysis the paired sample t test and the independent sample t test were used.Treatment was completed for 6 months. There were improvement in the lipid profile in both doses (p=0.05). No significant differences were found in lipid profile between the two groups except in cholesterol level (P-value 0,01) while regarding the remaining variables(TG, HDL, LDL, F.B.S,SGOT,SGPT) P-values were not statistical significantly different(0.776, 0.201, 0.383, 0.256, 0.832, 0.449 respectively). Atorvastatin lowered LDL by 23% as well as improved HDL by 6,3%. The reductions of lipid profile with atorvastatin were large with both doses (20 and 40 mg). Furthermore there is no difference between the two doses. Therefore it is recommended to start with the lower dose.

Keywords: Dyslipidemia, atorvastatin, diabetes mellitus, coronary heart disease

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 [1].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[1,2]. Statin decrease LDL and cholesterol synthesis. Furthermore in high doses it reverse plaque growth and plaque stabilization. Further effects include restoration of normal endothelial function[3]. Statins may reduce mortality amongst chronic obstructive pulmonary disease (COPD) and reduce pulmonary artery pressure through inhibition of guanosine triphosphatases, lowers serum cytokines such as IL-6 [4-7].

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A number of studies compared high and low doses of statin therapy in risk reduction. These show that higher doses are more effective in reduction of myocardial infarctions/coronary death (by 16%) and stroke (18%)but associated with increased risk of myopathy and elevated transaminases [8]. Evaluation of potency of statins in vascular disease showed that rosuvastatin is the most potent statin followed by atorvastatin [9]. Delay in titrating statin therapy to the optimal dose may lead to an increased risk of atherosclerosis-related events in high-risk patients [10]. A comparison between various statins on LDL and cholesterol in the area of safety and price found that atrovastatin is the best one[11]. Statin therapy significantly decrease the risk of ischemic stroke and transient ischemic attack (TIA) in patients with recent cerebrovascular disease[12,13]. Aggressive treatment of dyslipidemia among diabetic prevents macrovascular complications. The first line of treatment for diabetic dyslipidemia usually statins due to the effect on inflammatory and fibrotic pathways[1,14]. Two studies have specifically addressed the question of whether statins associated with diabetes. The first meta-analysis concluded high-dose statins was associated with one additional case of type II diabetes for every 498 patients treated; whereas one major

cardiovascular event was prevented for every 155 patients treated. The second study analyzed data from 153,840 postmenopausal women. The study found that women taking statins had a 48% increased risk of diabetes compared to women not taking statins. However the benefit of statins appears to substantially outweigh the risk[15,16].

Statin therapy reduce LDL-C levels and, subsequently reduced vascular events among patients with a broad range of cerebrovascular(CV) risk factors, including T2DM[17-19]. The role of statins on patients with nephritic syndrome was evaluated. The studies concluded that statin administration is associated with a lower risk of venous thromboembolism in patients with nephritic syndrome[20,21].

In this study we aimed to compare between atorvastatine 20 mg and 40 mg in treatment of dyslipidemia. Evaluate the outcome of the drug on kidney function, liver function, random blood sugar and lipid profile.

Materials and Methods

Methodology

The study conducted in the Indonesian hospital in Gaza between 10/6/2015 –10/3/2016 designed a single randomized clinical trial. All outpatients diagnosed first time with dyslipidemia based on laboratory data along with cardiovascular or diabetes in the last three months were included. The total numbers of patients were 55 patients. The exclusion criteria were patients with normal lipid profile, pregnant women, children below 18 years age or patients over 75 years old and those within one week of myocardial infarction. The patients were randomly allocated to one of two groups. Base line data for each patient were taken regarding age, weight, gender, lipid profile, kidney function test, liver function test and fasting blood sugar. All patients informed about the study and informed that he can withdraw at any time. The patients in the first group (27 patient) received a fixed dose (20 mg/day) of atrovastatin (lipidon)^{R}, the second group (28 patient) received a fixed dose (40 mg/day) of atrovastatin (lipidon)^{R}. No adjustments of the dose have made during the entire period of the study. Both groups were observed for the treatment period of the study. The patients informed to take the drug at 10 PM. No directions were given regarding diet. Monthly follow up was done to confirm that the patients receive the medication. The data collected, tabulated and analyzed with SPSS version 20.The paired t test was used to compare the effect of the drug on lipid profile and the independent sample T- test is used to compare between means. The value of P<0,05 were considered statistically significant and the confidence interval (CI) is 95%. The study approved by HELSINKI committee in Gaza Strip.

Results

The initial number was 55 patients, three of them were excluded due to incompletion of treatment(see figures and tables files)

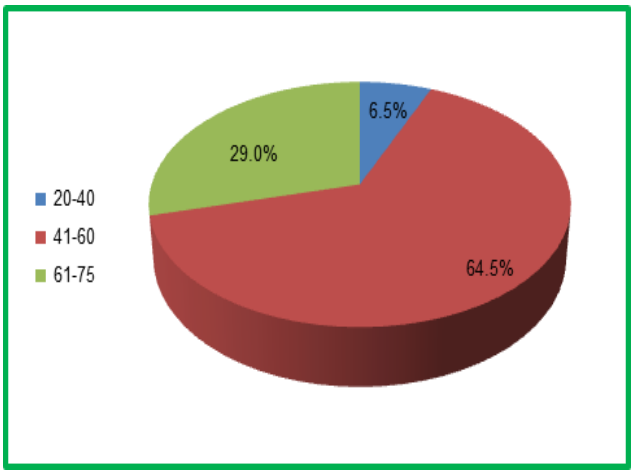

Figure (1) distribution of patients based on age, 6.5% age range from (20-40) year, 64.5% age range from(41-60) year and 29% (61-75) year.

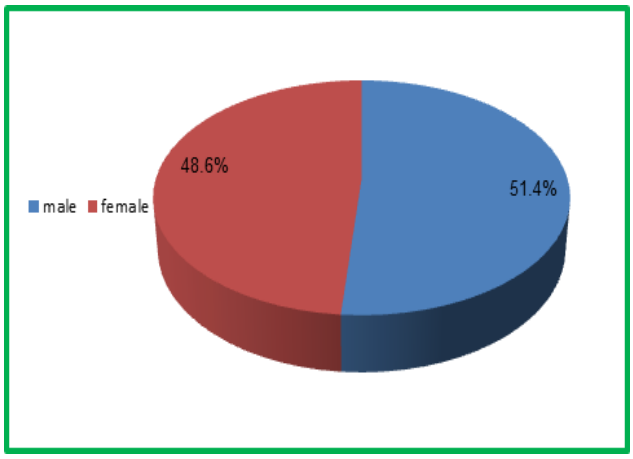

Figure 2. distribution of patients based on gender, 48.6% females and 51.4 % males.

Table 1. Normality test shows that the data only obey normal distribution when the significance is more than 0.05.

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
chole_before	.117	18	.200*	.961	18	.614
TG_before	.170	18	.179	.856	18	.011
HDL_before	.270	18	.001	.711	18	.000
LDL_before	.174	18	.158	.940	18	.293
HDL_after	.127	18	.200*	.974	18	.873
LDL_after	.158	18	.200*	.961	18	.628
Cr_before	.336	18	.000	.839	18	.006
F.B.S_before	.276	18	.001	.751	18	.000
SGOT_before	.331	18	.000	.525	18	.000
SGPT_before	.283	18	.001	.631	18	.000

Paired sample t test

Table 2. Comparison the effect of 20 mg & 40mg atorvastatin before & after **,** the P-value statistically significant in the cholesterol level, TG and LDL level.

dose	Variable	95% Confidence Interval of the Difference		t	p-value
		Lower	Upper		
20 mg	chole_before - chole_after	27.24473	71.22586	4.746	0.000
40 mg	chole_before - chole_after	21.44372	183.61510	2.681	0.016
20 mg	TG_before - TG_after	23.91151	139.50026	2.997	0.009
40 mg	TG_before - TG_after	88.62886	255.84173	4.367	0.000
20 mg	LDL_before - LDL_after	-3.40267	68.60267	2.048	0.071
40 mg	LDL_before - LDL_after	16.79234	77.65210	3.579	0.007

Table (3) Comparison the effect of 20 mg & 40mg atorvastatin before & after, the P-value statistically not significant in HDL, Cr, F.B.S, SGOT and SGPT.

dose	Variable	95% Confidence Interval of the Difference		t	p-value
		Lower	Upper		
20 mg	HDL_before - HDL_after	-4.05889	1.23536	-1.131	0.275
40 mg	HDL_before - HDL_after	-10.51292	13.01292	.234	0.819
20 mg	Cr_before - Cr_after	-.05140	.11023	.772	0.452
40 mg	Cr_before - Cr_after	-.31666	.01078	-1.980	0.065
20 mg	F.B.S_before - F.B.S_after	-4.78660	39.37483	1.660	0.116
40 mg	F.B.S_before - F.B.S_after	-37.34537	46.63948	.235	0.817
20 mg	SGOT_before - SGOT_afte	-1.87997	9.76232	1.435	0.170
40 mg	SGOT_before - SGOT_afte	-6.25633	2.96222	-.758	0.460
20 mg	SGPT_before - SGPT_after	-1.24027	9.12262	1.612	0.126
40 mg	SGPT_before - SGPT_after	-1.88529	7.65000	1.282	0.218

Independent sample t test

Table 4. Comparison of the effect of atorvastatin 20 mg and atorvastatin 40 mg after treatment on serum (Cholestrol, TG, HDL, LDL, Cr, F.B.S, SGOT and SGPT) level . P-value is not statistically significant for both doses except in cholesterol variable.

Dose		Mean	S.D	t	P-value
chole_after	20.00	191.82	33.59	2.683	0.011
	40.00	162.29	30.51		
TG_after	20.00	191.71	58.51	.287	0.776
	40.00	182.82	113.24		
HDL_after	20.00	41.94	4.49	1.306	0.201
	40.00	39.40	6.45		
LDL_after	20.00	113.30	31.55	0.894	0.383
	40.00	99.40	37.70		
Cr_after	20.00	0.96	0.16	-1.053	0.302
	40.00	1.04	0.28		
F.B.S_after	20.00	117.82	41.85	-1.156	0.256
	40.00	140.24	68.14		
SGOT_after	20.00	29.00	21.99	0.214	0.832
	40.00	27.76	9.04		
SGPT_after	20.00	31.65	25.09	0.766	0.449
	40.00	26.12	16.03		

Discussion

Dyslipidemia considered the most important risk factor for cardiovascular, cerebrovascular and diabetes and other diseases. Statins are the first line drug therapy in treatment dyslipidemia. There is agreement for use of the maximum dose in myocardial infarction (MI) and acute coronary syndrome (ACS) but there is controversy about the optimum dose for other indications. This study attempts to find the optimum dose of atorvastatin. The study designed randomized clinical trial since it is the most strict study and the analysis power of this study is 90%. Therefore comparison was made between atorvastatin 20 mg and atorvastatin 40 mg. The age distribution showed that the most affected age group (41-60) years old and the least affected group are those of younger age. This is similar to word distribution patients, since dyslipidemia affects older ages and less commonly seen in younger ages except those with familial hypercholestorlemia.

According to gender distribution dyslipidemia affected males more than females (52% versus 48%) respectively, this may be due to estrogen effect which have protective effect to the women against cardiovascular disease. The results shows that the data obey the normal distribution when the significance value was more than 0.05 and deviated away when the significance is lower than 0.05 table (1).

Based on the results obtained from (paired t- test) shown in tables (2-3) both doses were effective in reducing

cholesterol, TG and LDL levels and there was statistical significance [95% CI, P-value less than 0,05]. The effect on HDL-C was not statistical significant, but the mean elevation on HDL-C was 6.5% which falls in the mean value of the effect of statins on HDL-C. The creatinine (Cr) clearance, fasting blood sugar (F.B.S), liver enzymes SGOT and SGPT was not reached statistical significance. According to these data atorvastatin was effective in both doses and there were no serious effects on liver function, kidney or blood sugar level. This may be due to short term of study(six months) and the diabetogenic effects of statins needs longer period, moreover these drugs only used when the liver function within normal range and should be discontinued if the liver enzymes elevated more than three times above normal. In our study all patients were within normal value of liver enzymes and none of them had deteriorated liver function. The independent sample t test shown in table (4) demonstrated no significant difference between the two groups on lipid profile except on cholesterol level (P- value 0,011) while the remaining variables (TG, HDL, LDL, Cr, F.B.S, SGOT, SGPT) P-value were not statistical significant[95% CI, P-value 0,05]. According to these result there is no significant difference between high and low dose of atorvastatin. The exception is that 40 mg dose was better in reducing LDL-C and its mean value was in the therapeutic range 99.4 mg/dl and total cholesterol (mean 161 mg/dl) but it was associated with more diabetogenic effect 140 mg/dl. These results added another proof on the diabetogenic effect of statins but it was more pronounced in those with higher dose.

Conclusion and recommendation

This study demonstrated no significant difference between high and low dose of atorvastatin. Therefore we recommend assessment of lipid profile and starting dose to be the lowest dose because it has the same effect and less side effect. This study to represent a base for other larger studies in this field.

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