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EFFECT OF SIMVASTATIN WITH, WITHOUT EZITIMIBE ON SERUM LIPID PROFILE IN HYPERLIPIDEMIC PATIENTS

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ABSTRACT

Hyperlipidemia one of risk factor facing the coronary heart patients .Its a study to evaluate the efficacy of vytorin 20 mg (simvastatin/ ezetimibe) 10/10mg versus simvastatin 20 mg in reducing total cholesterol (Ch.), triglyceride (TG), low density lipoproteins (LDL) and very low density lipoproteins (VLDL). This study included 90 subjects, 30 healthy subjects and 60 untreated hyperlipidemic patients. The patients divided into two groups. The first group included 30 patients treated with Vytorin (2omg/day) which is a combination of two drugs (simvastatin 10mg+ezitimibe 10mg) taken daily at night and the second group included 30 patients treated with simvastatin 20mg/day alone .Serum lipid profile were measured after 12 hrs fasting in 3 intervals: before, after 6 weeks and 12 weeks of treatment.

It has shown that in two groups patients which treated with simvastatin 20 mg and vytorin 20 mg, reducing the level of serum cholesterol, triglycerides, low density lipoproteins and very low density lipoproteins while high density lipoproteins were increased in both groups. Conclusion: Combination of two drugs vytorin 20 mg ((simvastatin/ ezetimibe) 10/10mg) daily is more effective than simvastatin 20 mg taken alone in treatment of hyperlipidemic patients.

Keywords: Simvastatin, Ezetimibe, Vytorin, Hyperlipidemic Patients

INTRODUCTION

A considerable number of patients at high cardiovascular risk and or with severely elevated low- density lipoprotein cholesterol (LDL-C), up taking statins but don't achieve the rigorous treatment targets recommended by European, Canadian and USA guidelines

[1]. Clinical trials results have demonstrated that combining ezetimibe with a statin more over effectively lowers LDL-C versus treatment with either of the individual components alone **[2]**. The ezetimibe and simvastatin in hyper cholesterolemia enhances atherosclerosis regression trial was probably the most widely published clinical study of the past decades **[3]**. The enhance trial designed in early 2000 by Jonn J. Kastein, MD, Ph.D one of the most prominent clinical trialsts in lipidology **[4]**. Evidence indicates that the beneficial effects of statins can be attributed to their lipid lowering ability as well as to additional benefits **[5]**.

Ezetimibe is a specific cholesterol absorbtion inhibitor that acts at the brush border of the small intestine ,blocking the absorption of dietary ,biliary cholesterol and plant sterols ,resulting in intracellular cholesterol depletion via the Niemann-pick C1 like transporter. Adding ezetimibe to statin therapy induces a 15% reduction in LDL levels compared with only 6 % achieved by doubling the dose of statins **[6, 7]**.

Simvastatin [butanoic acid, 2, 2-dimethyl, 1, 2, 3, 7, 8 a-hexahydro-3,7-dimethyl -8-[2(tetrahydro-4-hydroxy-6-oxo-24-pyran-2-y1)-ethyl]-1-N aphthalenylester, is a lipid – lowering agent that is derived synthetically from fermentation products of fungal isolate *A. terrus.*

After oral ingestion simvastatin, which is an inactive lactone, is hydrolyzed to corresponding β-hydroxy acid leading to the inhibition of 3-hydroxy 3-methylglutaryl coenzyme A.(HMG-Co A) reductase **[8]**.

Primary hypercholesterolemia the most common form of hyperlipidemia, is defined as a total cholesterol level of 240 to 350 mg/dl. This condition is caused by a mutation of DNA (e.g. guanin to cytosine) on the LDL-receptor and its greatly affected by excessive consumption of saturated fats and high intakes of cholesterol and trans fatty acids **[9]**.

Ezitimibe is presently the only medication in a new category of cholesterol –lowering agents that inhibits small intestinal absorption and decreases lipoproteins associated with high total cholesterol .A peak response is seen in healthy subjects with hypercholesterolemia when they take E/S orally for two weeks. This maximal response is maintained while therapy continues **[10]**

The plasma drug concentrations attained are equivalent to those achieved when ezitimibe and simvastatin are administered concurrently as separate agents, disturbances of glucose metabolism accompanied by insulin resistance are pro-inflammatory conditions which may

accelerate atherosclerotic process **[11]**. Diabetic populations are considered at high cardiovascular risk and strict control of lipoprotein concentrations is recommended **[12, 13]**. From above its important to study the comparison effect of

/Semvastatin and vytorin on hyperlipidemic patients in Baghdad area to assess percentage of changes along two different periods of treatment and with least concentrations.

MATERIALS AND METHODS

Eligible subjects were aged35-75 years of age, weighed 68-82kg. They were stable blood pressure and no evidence of cardiovascular, hepatic or renal diseases in addition were not taking anti-inflammatory agents or others interfering with lipid or glucose metabolism, all subjects received life style, diet counseling and treatment compliance recommendations.

subjects subdivided into three groups, first (30) healthy subjects received no drug , second (30) subjects received 20 mg Simvastatin ,third were received vytorin 20mg ((simvastatin+ezitimibe)10/10mg). Serum was separated and total cholesterol (TC), Triglycerides (TG), high density lipoproteins(HDL)was measured by enzymatic colormitrec methods after 12 hrs over night fasting by using analyzer (selectra -11,Micro Germany).LDL-cholesterol was calculated mathematically from the total cholesterol ,triglycerides and HDL-cholesterol concentrations

LDL-cholesterol (mmol/L)=cholesterol-TG/2.2-HDL[14] also VLDL-cholesterol was calculated mathematically as following from the triglycerides

VLDL-cholesterol (mmol/L)=TG/2.2[15]

Statistical Analysis

In each group of treatment, descriptive analysis using mean and standard deviation for TC, TG, HDL, LDL and VLDL variables and independent t-test to compare the control and before treatment groups. Percentage of change after 6 and 12 weeks of treatment was compared between the two groups of treatment using independent t-test. Statistics was done using SPSS (Statistical Package for Social Sciences) version 17 was used for analysis.

RESULTS

Baseline demographics and clinical characteristics were generally similar between treated groups. The results revealed that the effect of combined drugs Ezitimibe/Simvastatin were more effective in lowering total cholesterol than up taking simvastatin mono therapy the mean ± SD of the treated groups by Ezitimibe+simvastatin demonstrate the lowering lipid profile from 1st period of treatment (6weeks).

After 6 weeks of treatment Ezi/Sim. 10/10 mg resulted in a significant reductions from treated baseline in LDL-C levels compared

with Sim. monotherapy /10 mg (means ±SD) of LDL-C were [,TC5.50±0.37, TG1.74±0.236, LDL-C 3.48±1.22, VLDL0.79± 0.107] versus [TC6.08±0.25,TG1.83±0.22,LDL4.458±0.46,VLDL0.83±0.98] simv./10mg respectively as shown in **Table 1**.

After the second period of treatment (12 weeks) there were significantly reduction in LDL-C, for treatment in using vytorin 20mg (means ±SD) [TC4.470±0.339,TG1.180 ±0.189,LDL2.588±0.917,VLDL0.536±0.862] versus [TC 4.770±0.292, TG 1.360±0.263, LDL 3.045±0.527, VLDL 0.618±119] when used sim./20 mg as shown in **Table 1, 2**. HDL-mean was not affected by doubling treatment vytorin as other lipid profile parameters, HDL from baseline 0.580±0.170 to 6weeks 0.950±0.133 while for 12 weeks it increased to 1.170±.0.126 as shown in **Table 1, 2**.

Percentage of change between 2 treated groups revealed that percentage of sim/ezi 10/10 were higher than percentages of Sim/20 mg after 6 weeks of treatment as shown in **Figure 1**. As well as percentage of change between 2 treated groups resulted in great increasment of sim/ezi. 10 /10 than percentage of changes of sim/20mg after 12 weeks of treatment as shown in **Figure 2**.

Table 1: Effect of Vytorin (Simvastatin +Ezitimibe) on Serum Total Cholesterol, Triglycerdides, High Density of Lipoproteins, Low Density of Lipoproteins, Very Low Density of Lipoproteins After 6 and 12 Weeks of Treatment

Parameters (Lipid profile)	Control	Before treatment	6weeks of treatment	12weeks of treatment
TC (mmol/L)	5.2400(±0.873)	7.010(±0.254)	5.500(±0.373)	4.470(±0.339)
TG (mmol/L)	1.540(±0.263)	2.780(±0.145)	1.740(±0.237)	1.180 (±0.189)
HDL (mmol/L)	1.230(±0.109)	0.580(±0.170)	0.950(±0.133)	1.170(±.0.126)
LDL (mmol/L)	3.235(±1.01)	5.166(±0.484)	3.481(±1.229)	2.588(±0.917)
VLDL (mmol/L)	0.70(±0.119)	1.264(±0.068)	0.791(±0.107).	0.536(±0.862)

Table 2: Effect of Simvastatin on Serum Total Cholesterol, Triglycerdides, High Density Lipoproteins, Low Density of Lipoproteins, Very Low Density of Lipoproteins After 6 and 12 Weeks of Treatment

Parameters (Lipid profile)	Control	Before treatment	After 6weeks of treatment	After 12weeks of treatment
TC(mmol/L)	5.240(±0.873)	6.850(±0.219)	6.080(±0.256)	4.770(±0.292)
TG(mmol/L)	1.540(±0.263)	2.610(±0.108)	1.830(±0.292)	1.360(±0.263)
HDL(mmol/L)	1.230(±0.109)	0.630(±0.126)	0.790(±0.117)	1.107(±0.128)
LDL(mmol/L)	3.310(±1.093)	5.035(±0.387)	4.458(±0.468)	3.045(±0.527)
VLDL(mmol/L)	0.700(±0.11851)	1.185(±0.047)	0.832(±0.098)	0.618(±119)

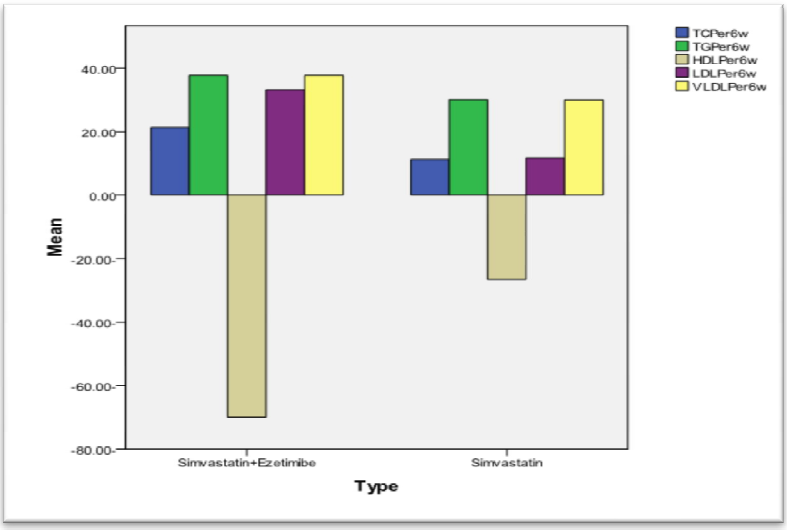

Figure 1: Effect of Simvastatin and Vytorin (Simvastatin+ Ezetimibe) Treatment on the Percentage of Changes in Lipid Profile Parameters After 6 Weeks of Treatment

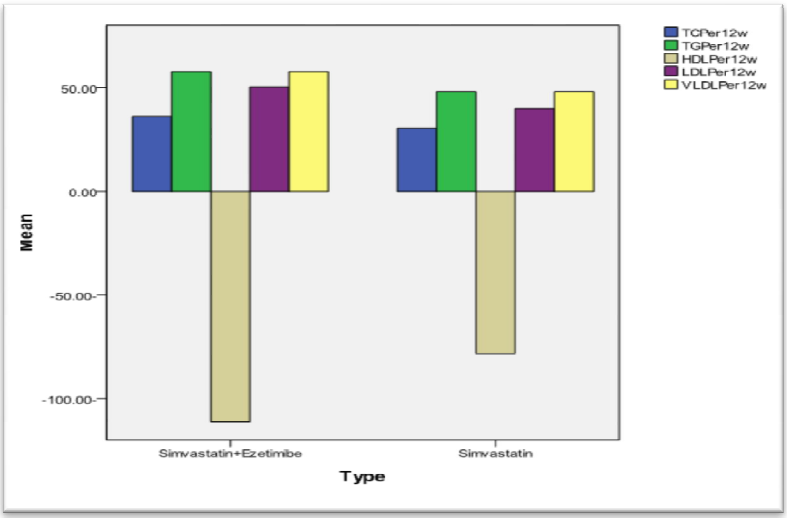

Figure 2: Effect of Simvastatin and Vytorin (Simvastatin+ Ezetimibe) Treatment on the Percentage of Changes in Lipid Profile Parameter After 12 **Weeks of Treatment**

DISCUSSION

This study provides further proof of the role of the vytorin ((simvastatin+ ezitimibe) 10/10mg) of lipid-lowering agent in improving the atherogenic lipid profile. The vytorin resulted in greater reductions in LDL-Cholesterol. Since simvastatin may be ineffective in reaching the target more options are desirable to optimize the management of hypercholesterolemic subjects. Changes in HDL-C & TG were similar between treated groups and these changes were consistent with results of previous trials comparing vytorin versus sim monotherapy in Coronary heart disease patients **[16]**. They are also generally consistent in patients with type two diabetes mellitus **[17]**. It has been established that adding ezi to sim monotherapy results in greater reductions in LDL-C and other lipids

compared with sim. Monotherapy, even when existing sim therapy is doublet **[18]**. Other study shows that the mean reductions in LDL-C was 8% greater with ezi./sim 10/40 mg compared with atorvastatin 40mg **[19]**. The vytorin versus Atorvastatin study which assessed subjects with hypercholesterolemia and established Coronary heart diseases ezi/sim 10/40 mg resulted in greater decrease in a 9% greater decrease in LDL-C compared with atorvastatin 40mg **[20]**. This variation between studies could be due to differences in study design or subject population **[21]**.

The current study consistent with **[19]** that the baseline LDL-C level values were determined prior to sim. monotherapy which would be potentially describe a smaller LDL-C reduction. In current study the percentage of those reaching a LDL-C cholesterol goal of 100 mg/dl. Increased from 30% induced by sim. monotherapy to 50% following the sim/ezi combination after 6 weeks of treatment.

Statins should be used as initial therapy for hyperlipidemia and titerated to the goal LDL-C level or to the maximally tolerated dose and that other drugs. Such as bile acid sequestrants, fibrates and niacin should be used in combination with statins before considering ezi **[22]** it was concluded that ezi. lowers LDL-C.

In summary the dual cholesterol-lowering mechanisms provided by ezi./sim. resulted in greater overall LDL-C lowering efficacy across dose ranges, better general LDL-C treatment goal attainment increased HDL-C efficacy averaged across dose ranges and at higher doses compared with atorvastatin monotherapy.

CONCLUSION

Vytorin a good choice of lowering lipid levels in hyperlipidemic patients. Time factor play a great role in lowering hypercholesterolemia and hyperlipidemia with producing beneficial effect of drugs. Other prospective studies including larger supply and higher medication doses may be necessary to produce best results.

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