



ORIGINAL RESEARCH

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## Evaluate the efficacy of Simvastatin and Fluvastatin in patients with hypercholesterolemia and their effect on liver functions

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### Abstract

The study was aimed to evaluate Simvastatin and Fluvastatin effects on patients with hypercholesterolemia. For 6 months, 141 patients administered Simvastatin (GpA), 100 administered Fluvastatin (GpB) and 100 fluctuated between them (GpC). Post treatment, in GpA, Triglycerides, total Bilirubin (T.BIL), Cholesterol and Low Density Lipoprotein (LDL) were significantly reduced. Alkaline Phosphatase (ALP) and Alanine Aminotransferase (ALT) elevated reduced in females and elevated in males. T.BIL reduced in both males and females. In GpB, Glutamytransferase elevated and Cholesterol and LDL reduced. Albumin elevated in females and reduced in males and the opposite in Triglycerides. Significant difference between age groups in Albumin, Globulin, and ALT was found. In GpC, Aspartate Aminotransferase (AST) elevated and ALT, Cholesterol, Triglycerides and LDL reduced in all patients. Albumin and ALT elevated in males and reduced in females. Significant difference between age groups in Albumin, T.BIL and AST was found. Fluvastatin or simvastatin had variable effects on lipid parameters in patients with hypercholesterolemia and associated with mild effect on liver. Simvastatin was more effective to reach antihypercholesterolemic goal. Effects were related to gender, age and continuation on the same medication. Patients lab data periodic monitoring during therapy is useful to reach antihypercholesterolemic goal and observe any serious liver parameters elevation.

**Keywords:** Hypercholesterolemia, simvastatin, fluvastatin, effect on liver functions

### Introduction

Lipid-lowering drugs are among the most prescribed medications in the world with more than 20 million people prescribed this class of drugs. Since the US Food and Drug Administration (FDA) approved Lovastatin in 1987, statins (3-hydroxy-3-methyl glutaryl coenzyme A [HMG-CoA] reductase inhibitors) have been the most widely used for the treatment of dyslipidemia to reduce the risk of cardiovascular disease. There has been considerable debate in the medical community regarding the clinical significance of the potential differences between the drugs in this class[1].

It is commonly supposed that statins act by blocking cholesterol synthesis through inhibition of HMG-CoA reductase is the first and rate-limiting step in cholesterol synthesis [2, 3]. Lowering plasma low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) level to the target value is considered essential in the treatment. Currently, 3-hydroxy-3-methylglutaryl coenzyme role in the treatment of hypercholesterolemia.

Various A (HMG-CoA) reductase inhibitors (statins) play a central statin trials have shown that lowering plasma cholesterol level in patients with statins can reduce coronary heart diseases (CHD) and total mortality risk [4-6].

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CoA) reductase inhibitors (statins) play a central role in statin trials have shown that lowering plasma cholesterol level in patients with statins can reduce coronary heart diseases (CHD) and total mortality risk [4-6]. In recent years, many patients and health professionals have questioned the safety of statins. There have been indications from the media and from clinical experience that some patients refuse to initiate statin therapy while others choose to withdraw from long-term statin treatment because of concerns about safety [7]. The importance of investigating hepatic adverse effects of drugs on the liver lies in the fact that drug-induced hepatotoxicity has become an important public health problem, contributing to more than 50% of acute liver failure cases [8]. Annually dozens of patients with drug induced hepatotoxicity were demonstrated, a fraction of whom requires immediate transplantation because of irreversible damages to their livers. The attention of studying drug hepatotoxicity had increased when a number of fatal hepatic toxicity cases were demonstrated with 2 drugs of the thiazolidinedione antidiabetic agents (troglitazone and rosiglitazone) which caused acute hepatic failure and severe hepatocellular injury [9-11]. The first clinical studies on HMG-CoA reductase inhibitors reported a low incidence of liver toxicity, but this was followed by observations of a large number of cases on statin therapy with hepatic toxicity [12]. Because of the less number of data concerning the hepatic toxicity of statins and comparing the activity of them, the present study was performed to evaluate the hepatic adverse effects and antihypercholesterolemic effect of statins on liver by measuring and follow up liver parameters in a number of hypercholesterolemic patients who received simvastatin and Fluvastatin.

## Material and Methods

This study was undertaken in Bahrain Defense Force Hospital (Military Hospital) in Bahrain. Ethical approval was obtained from the hospital ethics committee.

### Criteria for patient selection

Inclusion Criteria:

- Male or female aged over 18.
- Patients who were just starting a statin treatment, who need to switch from current therapy to a statin medication, or who are receiving dosage adjustment of statin as judged by the physicians.
- Patients have no history of liver disease.

Exclusion Criteria:

- Pregnancy or breast feeding.
- Patients with contraindications to the use of certain statins as hypersensitivity.
- Severe renal disease or renal dysfunction.
- Chronic liver disease or liver function impairment (hepatitis, cirrhosis, obstructive jaundice).
- Patients who took any other type of statin before as a treatment for Hypercholesterolemia.

### Patients

The selected patients were randomly divided into three groups of hypercholesterolemic 150 patients each. The patients were asked to take part in the study after explaining to them their role in the study. Consent was obtained from each patient before enrolling in the study. Any patient how withdraw from the study at any time his

data was removed.

Group I: Patients on Simvastatin therapy administered Simvastatin therapy (Simvorrnanbaxy- laboratories limited, India) to lower their high blood lipid concentration. Simvastatin dose was 20 mg once daily at bedtime.

Group II: Patients on Fluvastatin therapy administered Fluvastatin therapy (Lescol XL - Novartis laboratories) to lower their high blood lipid concentration. Fluvastatin dose was 80 mg once daily at bedtime.

Group III: Patients on Fluctuate use therapy administered mixed Simvastatin and Fluvastatin randomly to lower their high blood lipid concentration. Simvastatin dose was 20 mg once daily at bedtime and Fluvastatin dose was 80 mg once daily at bedtime randomly fluctuate between them during the study period.

### Methods

The patients were followed up through the database system and medical record files collecting, the laboratory results of lipid parameters tests and liver functions tests on starting treatment and 6 months post treatment using the next laboratory parameters:

Total Protein (TP) g/L using BIURET Method

Albumin (ALB) g/L using DYE-BINDING-BCG (Bromocresol Green) Method

Globulin (GLO) g/L BY CALCULATION from formula (Globulin = Total Protein- Albumin)

Total Bilirubin (T.BIL) and Direct Bilirubin (D.BIL)  $\mu$ mol/L using Diazo Method

Alkaline Phosphatase (ALP) IU/L using Colorimetric Method

Aspartate Aminotransferase (AST) IU/L using IFCC without pyridoxal phosphate activation,

Alanine Aminotransferase (ALT) IU/L using IFCC without pyridoxal phosphate activation

G-Glutamyltransferase (GGT) IU/L using Enzymatic Colorimetric Method

Low-density lipoprotein (LDL) and High-density lipoprotein (HDL) mmol/L using Roche HDL-CHOL Plus Method

Triglycerides (TG) and Cholesterol (CHO) mmol/L using Enzymatic Colorimetric Method

### Statistical methods

Descriptive statistics were presented for the endpoints and for a comparison between endpoints Wilcoxon test, Kruskal Wallis Test, chi-square Test, Student t- test and one way ANOVA were used to compare the results of the three groups. Statistical package for social science (SPSS) software version 19 (SPSS Inc., Chicago, IL) was used.

### Results

A total of 450 were enrolled in the study, 341 (165 females) patients completed the study. Their ages ranged from 32 to 91 years. 141 (66 females) patients were taking Simvastatin their ages ranged from 32 to 86 years as GpA, 100 (49 females) were taking Fluvastatin their ages ranged from 35 to 91 years as GpB and 100 (50 females) fluctuated randomly between both of Fluvastatin and Simvastatin their ages ranged from 32 to 86 years as GpC. Table 1 shows the effects of the three treatment groups on all patients liver function and blood tests.

**Table 1.** Effects of the three treatment groups on all patients

Test	Simvastatin 20mg				Fluvastatin 80mg				Fluctuation			
	Before	After	p-value (t-test)	Mean of Change %	Before	After	p-value (t-test)	Mean of Change %	Before	After	p-value (t-test)	Mean of Change %
	Mean $\pm$ SD	Mean $\pm$ SD			Mean $\pm$ SD	Mean $\pm$ SD			Mean $\pm$ SD	Mean $\pm$ SD		
TP	71.8 $\pm$ 5.5	72.7 $\pm$ 5.4	0.165	1.40%	73.2 $\pm$ 6	72.3 $\pm$ 6	0.268	-0.70%	73.9 $\pm$ 5.1	74 $\pm$ 7.1	0.732	-0.20%
ALB	39.8 $\pm$ 3.9	40.7 $\pm$ 4.5	0.074	2.30%	40.6 $\pm$ 5	40.8 $\pm$ 4.3	0.833	0.60%	40.8 $\pm$ 4.4	40.3 $\pm$ 4.7	0.142	-0.90%
GLO	32.3 $\pm$ 5.7	32.2 $\pm$ 5.2	0.975	1.70%	32.6 $\pm$ 5.6	31.5 $\pm$ 5.9	0.111	-2.00%	33 $\pm$ 4.7	33.3 $\pm$ 4.8	0.971	1.00%
T.BIL	10.9 $\pm$ 5.8	9.3 $\pm$ 5.3	0.010*	-3.70%	9.3 $\pm$ 5.5	10.3 $\pm$ 7.9	0.285	8.10%	7.8 $\pm$ 3.8	7.2 $\pm$ 3.4	0.104	2.30%
D.BIL	4.8 $\pm$ 9	2.7 $\pm$ 1.2	0.165	12.50%	2.7 $\pm$ 1.4	3 $\pm$ 1.6	0.367	28.90%	2.3 $\pm$ 0.9	2 $\pm$ 0.6	0.101	-2.50%
ALP	73.8 $\pm$ 22.8	73.8 $\pm$ 23.3	0.973	2.70%	72.4 $\pm$ 21.9	76.1 $\pm$ 27.4	0.060	8.40%	76.4 $\pm$ 21.7	74 $\pm$ 24.3	0.183	-1.00%
ALT	26 $\pm$ 16.5	24.5 $\pm$ 11.3	0.341	11.20%	25.9 $\pm$ 18.6	25.8 $\pm$ 13.8	0.943	11.30%	24.3 $\pm$ 11.1	22 $\pm$ 8.6	0.045*	-0.90%
GGT	36.7 $\pm$ 26.7	36.9 $\pm$ 28.7	0.577	16.90%	34.3 $\pm$ 19.4	40.1 $\pm$ 26.2	0.004**	21.40%	39 $\pm$ 22.6	42 $\pm$ 33	0.105	13.20%
AST	19.9 $\pm$ 7.9	19.7 $\pm$ 7	0.365	17.50%	20.5 $\pm$ 10.9	19.5 $\pm$ 6.1	0.920	4.20%	17.5 $\pm$ 5.6	18.8 $\pm$ 5	0.010*	13.50%
CHO	5.5 $\pm$ 1.1	4.5 $\pm$ 1	<0.001***	-15.50%	6.3 $\pm$ 5.7	4.7 $\pm$ 1	0.006**	-16.30%	5.8 $\pm$ 1.2	4.9 $\pm$ 1.3	<0.001***	-15.10%
TG	2.3 $\pm$ 2.8	2 $\pm$ 2.1	0.007**	-0.10%	2.3 $\pm$ 1.4	2.1 $\pm$ 2.2	0.353	-1.00%	2.2 $\pm$ 1.2	1.8 $\pm$ 1	<0.001***	-5.90%
LDL	3.6 $\pm$ 0.9	2.8 $\pm$ 0.9	<0.001***	-20%	3.7 $\pm$ 1	2.9 $\pm$ 0.7	<0.001***	-16.90%	3.9 $\pm$ 1.1	3.1 $\pm$ 1	<0.001***	-16.70%
HDL	1.2 $\pm$ 0.3	1.2 $\pm$ 0.8	0.633	6.10%	1.3 $\pm$ 0.8	1.2 $\pm$ 0.3	0.477	3.80%	1.2 $\pm$ 0.3	1.2 $\pm$ 0.3	0.837	2.50%

\* p&lt;0.05, \*\* p&lt;0.01 and \*\*\* p&lt;0.001

**Table 2.** Effects between genders within each of the three treatment groups

Test	Simvastatin 20mg			Fluvastatin 80mg			Fluctuation		
	Male	Female	p-value(t-test)	Male	Female	p-value(t-test)	Male	Female	p-value(t-test)
	Mean $\pm$ SD	Mean $\pm$ SD		Mean $\pm$ SD	Mean $\pm$ SD		Mean $\pm$ SD	Mean $\pm$ SD	
TP	72.6 $\pm$ 6.1	72.8 $\pm$ 4.7	0.858	72.6 $\pm$ 5.7	72.1 $\pm$ 6.3	0.743	74.2 $\pm$ 7.6	73.7 $\pm$ 6.6	0.776
ALB	40.8 $\pm$ 5	40.5 $\pm$ 4	0.703	42.1 $\pm$ 4.1	39.6 $\pm$ 4.2	0.007**	42.4 $\pm$ 4.1	38.2 $\pm$ 4.2	<0.001***
GLO	31.9 $\pm$ 5.2	32.5 $\pm$ 5.3	0.506	30.5 $\pm$ 5.4	32.3 $\pm$ 6.3	0.168	32.5 $\pm$ 4.5	34.1 $\pm$ 5	0.107
T.BIL	10.8 $\pm$ 5.8	7.8 $\pm$ 4.1	0.002**	13.2 $\pm$ 9.5	7.7 $\pm$ 5	0.002**	8.3 $\pm$ 3.5	6.1 $\pm$ 2.9	0.003**
D.BIL	3.1 $\pm$ 1.1	2.2 $\pm$ 1.1	0.100	3.4 $\pm$ 1.6	2.1 $\pm$ 1.1	0.043	2 $\pm$ 0.6	2.1 $\pm$ 0.5	0.880
ALP	69.1 $\pm$ 17.6	78.9 $\pm$ 27.5	0.016*	75.6 $\pm$ 26.8	76.7 $\pm$ 28.3	0.834	75.7 $\pm$ 27.1	72.3 $\pm$ 21.2	0.511
ALT	28.1 $\pm$ 11.8	20.6 $\pm$ 9.2	<0.001***	30.2 $\pm$ 16	21.2 $\pm$ 9.3	0.001**	25.8 $\pm$ 8	18.1 $\pm$ 7.5	<0.001***
GGT	39.6 $\pm$ 26.7	34.2 $\pm$ 30.5	0.287	43.3 $\pm$ 22	36.8 $\pm$ 29.8	0.221	51 $\pm$ 40.6	32.6 $\pm$ 18.7	0.006**
AST	20.8 $\pm$ 8.2	18.6 $\pm$ 5.5	0.113	20.6 $\pm$ 6.4	18.5 $\pm$ 5.6	0.137	20.5 $\pm$ 5.7	17.4 $\pm$ 3.9	0.011*
CHO	4.4 $\pm$ 1.1	4.7 $\pm$ 0.8	0.101	4.7 $\pm$ 1	4.7 $\pm$ 1	0.929	4.6 $\pm$ 1.1	5.1 $\pm$ 1.4	0.049*
TG	2.2 $\pm$ 2.7	1.8 $\pm$ 1	0.358	2.8 $\pm$ 2.8	1.5 $\pm$ 0.6	0.001**	2 $\pm$ 1	1.7 $\pm$ 0.9	0.153
LDL	2.8 $\pm$ 1	2.9 $\pm$ 0.8	0.331	2.8 $\pm$ 0.7	3 $\pm$ 0.8	0.247	2.9 $\pm$ 0.7	3.3 $\pm$ 1.1	0.062
HDL	1.2 $\pm$ 1	1.2 $\pm$ 0.5	0.925	1.1 $\pm$ 0.3	1.3 $\pm$ 0.3	<0.001***	1.1 $\pm$ 0.2	1.3 $\pm$ 0.3	<0.001***

\* p&lt;0.05, \*\* p&lt;0.01 and \*\*\* p&lt;0.001

**Table 3.** Effects of age within each of the three treatment groups

Test	Simvastatin 20mg				Fluvastatin 80mg				Fluctuation			
	31-45 years	46-60 years	>60 years	p-value (Kruskal Wallis Test)	31-45 years	46-60 years	>60 years	p-value (Kruskal Wallis Test)	31-45 years	46-60 years	>60 years	p-value (Kruskal Wallis Test)
	Mean ±SD	Mean ±SD	Mean ± SD		Mean ±SD	Mean ±SD	Mean ± SD		Mean ± SD	Mean ± SD	Mean ± SD	
<b>TP</b>	73.5 ± 4.1	73.2 ± 5.8	71.9 ± 5.6	0.291	71 ± 5.2	72.7 ± 6.6	72.3 ± 5.7	0.683	70.8 ± 11.8	74.9 ± 5.2	74.1 ± 6.3	0.762
<b>ALB</b>	40.2 ± 3.4	42 ± 4	39.5 ± 5.1	0.027*	42.9 ± 4.1	42.1 ± 3.6	38.9 ± 4.4	0.002**	41.8 ± 6.7	41.4 ± 3.8	38.1 ± 3.8	<0.001***
<b>GLO</b>	33.3 ± 5.7	31.7 ± 4.7	32.2 ± 5.5	0.378	28.3 ± 2.5	30.7 ± 5.9	33.1 ± 6.2	0.016	30.8 ± 3.6	33.3 ± 4.7	34.4 ± 5.1	0.053
<b>T.BIL</b>	8 ± 4.3	9.4 ± 4.9	9.9 ± 6	0.441	8.8 ± 6.6	10.8 ± 10.3	10.2 ± 5.2	0.412	8.7 ± 4	6.1 ± 2.1	7.8 ± 4	0.027*
<b>D.BIL</b>	2.3 ± 1.1	2.8 ± 1.5	2.5 ± 0.8	0.312	3.2 ± 1.5	3.2 ± 1.8	2.2 ± 0.6	0.374	2.2 ± 0.5	1.8 ± 0.6	2.3 ± 0.4	0.234
<b>ALP</b>	72 ± 21.4	71.8 ± 20.1	77.1 ± 27.6	0.929	81.7 ± 37.1	75.4 ± 23.2	74.9 ± 27.9	0.945	70.7 ± 15.4	69.1 ± 22.2	82.8 ± 28.9	0.053
<b>ALT</b>	24.1 ± 9.5	27.3 ± 11.6	21.3 ± 11	0.004**	34.9 ± 19.6	27.6 ± 13.3	20.7 ± 9.5	0.007**	24.2 ± 10.9	23.3 ± 8.9	19.1 ± 6	0.085
<b>GGT</b>	40.9 ± 29	36.4 ± 21.2	35.6 ± 36	0.088	50 ± 30.5	41.6 ± 28.3	35.1 ± 21.5	0.141	47.4 ± 21.7	37.3 ± 23.4	45.8 ± 46.7	0.175
<b>AST</b>	19.3 ± 7.1	21 ± 7.8	18.4 ± 5.9	0.119	20.8 ± 8.2	20.7 ± 6	17.9 ± 5.1	0.165	18.4 ± 5.1	20.3 ± 5	17 ± 4.6	0.027*
<b>CHO</b>	5 ± 0.8	4.6 ± 1	4.3 ± 0.9	0.01**	4.7 ± 1.1	4.6 ± 1	4.7 ± 0.9	0.921	5.4 ± 1.4	4.7 ± 1	4.9 ± 1.4	0.194
<b>TG</b>	1.7 ± 0.6	2.4 ± 3	1.6 ± 0.7	0.507	2.1 ± 1.5	2 ± 1.3	2.3 ± 3	0.709	2 ± 0.8	1.8 ± 1.1	1.8 ± 1	0.292
<b>LDL</b>	3.1 ± 0.8	2.9 ± 0.9	2.6 ± 0.8	0.099	2.8 ± 0.7	2.9 ± 0.6	2.9 ± 0.8	0.942	3.5 ± 1.3	2.9 ± 0.7	3.2 ± 1.1	0.150
<b>HDL</b>	1.2 ± 0.4	1.3 ± 1.1	1.1 ± 0.3	0.306	1.2 ± 0.2	1.2 ± 0.4	1.2 ± 0.3	0.627	1.3 ± 0.3	1.2 ± 0.3	1.1 ± 0.2	0.406

\* p<0.05, \*\* p<0.01 and \*\*\* p<0.00.

## Discussion

In contrast to most of the previous studies, this study quantified the differences and similarities of Simvastatin and Fluvastatin, including efficacy and safety, assessed in head-to-head comparison trials and provided pooled estimates where possible. The quantitative results of the lipid-lowering effect of each statin could serve as a quick guide for clinicians. This study identifies heterogeneity among studies and areas with insufficient data where future studies could be focused. The results of the present study indicated significant differences between Simvastatin and Fluvastatin in efficacy and toxicity.

The data of Simvastatin effect obtained in the present study indicate statically significant reductions were found among TG (-0.1%), CHO (-15.5%) and LDL (-20%) and mild but not significant elevation of HDL (6.1%). The data of Fluvastatin effect shows statically significant reductions among CHO (-16.30%) and LDL (-16.90%) that confirm results obtained from other studies [13-16] but with little difference in change percentage. This may be due to the difference in the culture, design and the study period. But in general, the lipid parameters results shows that the Simvastatin is more affective to reduce the LDL level than Fluvastatin and these results are in consistence with those obtained in many studies [16, 17]. However in Fluvastatin group there were statically significant reductions in age range 31-45 years (-32.30%) than the other groups and that opposite the results obtained by Bruckert et al [18]. That may be due to difference in culture and study design.

Generally in Simvastatin and Fluvastatin groups elevations of most

of measured hepatic parameters in the current study were observed. This may indicate that the pattern of hepatotoxicity caused by both of the used drugs is hepatocellular damage (elevation of AST and ALT) and cholestasis (elevation of ALP). However in Simvastatin group statically significant reductions were found among T.BIL, but statically significant elevation was found among ALP in female and reduction in male and more elevation found in ALP in patients >60 years comparing with other age groups. Review of the literature demonstrated controversial effects of Simvastatin on cholesterol and hepatic function, some studies reported an elevations of liver parameters during Simvastatin therapy [12,19-23] whereas others studies showed that Simvastatin has no effect on liver parameters [24,25]. Regarding the fluctuation group, in general for all patients there was significant effect on the lipid parameters less than the use of Simvastatin or Fluvastatin separately. Also there was an elevation of ALT, and significant reduction of LDL in male than in females and no relation between the age and the effect on lipid and liver parameters. No studies could be found in the literature which involves comparison of the effect of fluctuation between these two drugs on lipid and liver parameters. Finally the present study showed more efficacy of Simvastatin over Fluvastatin in lipid lowering but non-significant differences between liver parameters of Simvastatin and Fluvastatin which may indicate that the effect of both Fluvastatin and Simvastatin on the liver may be similar.

## Conclusions

The majority of patients receiving Fluvastatin can be successfully converted to Simvastatin without loss of lipid control. In many patients, LDL levels may decrease significantly with this

conversion. Simvastatin was more effective than Fluvastatin to reach the antihypercholesterolemic goal. The effect was related to the variables of gender, age, and continuation on the same medication. Periodic monitoring of the lipid parameters and biochemical hepatic parameters during therapy with Fluvastatin and Simvastatin may be of value to reach the antihypercholesterolemic goal and observe any serious elevation of liver parameters.

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